Clinical Effectiveness of Tailored E-coaching in Reducing Cardiovascular Risk Assessed Using Cardiovascular Imaging and Functional Assessment - A Primary Prevention Trial in Moderate to High Risk Individuals

Dr. Mohmed Yunus Khanji MRCP, MB BCh & BAO (Honours)

A dissertation submitted in partial fulfilment of the requirements of the degree of

Doctor of Philosophy

Of the

University of London

Centre for Advanced Cardiovascular Imaging

NIHR Cardiovascular Biomedical Research Unit at Bart's

William Harvey Research Institute

Queen Mary University of London

Statement of Originality

I, Mohmed Yunus Khanji, confirm that the research included within this thesis is my own work or that where it has been carried out in collaboration with, or supported by others, that this is duly acknowledged below and my contribution indicated. Previously published material is also acknowledged below.

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Details of collaboration and publications

Dr Redha Boubertakh provided programming and physics support related to the results in the CMR sub study chapter.

Professor Myriam Hunink and colleagues from Erasmus Medical Centre supported me with the systematic reviews process.

The HAPPY Globally foundation founders Professor Jagat Narula and Professor Leonard Hofstra along with the website technical team for helping to develop the HAPPY London Programme. Froukje Dijk and Rob Reintjens provided their information technology expertise in setting up the HAPPY London website and research administrative page. They helped to deal with the many technical issues that I encountered with the web system and provided the extracted data from the research web tool that we developed for this study.

Chapter 5

Cardiovascular Risk Assessment: A Systematic Review of Guidelines.
Mohammed Y. Khanji, MB, BCh; Vinícius V.S. Bicalho, MD; Claudia N. van Waardhuizen, MSc; Bart S. Ferket, PhD; Steffen E. Petersen, DPhil; M.G. Myriam Hunink, PhD. Accepted for publication ***Annals of Internal Medicine*** August 2016

Abstract

Cardiovascular disease remains one of the leading causes of mortality globally. Innovative techniques are required to tackle its anticipated rise due to rising obesity, diabetes and an ageing population. Personalised electronic coaching (e-coaching) using the Internet and emails may help motivate healthier living and be of clinical benefit in complementing current programmes for cardiovascular risk reduction.

I investigated whether personalised e-coaching on top of SOC was more clinically effective than SOC alone, in reducing cardiovascular risk in asymptomatic individuals with high cardiovascular risk. I lead a randomised controlled trial of 402 participants using robust surrogate markers to identify change over 6 months. I assessed the feasibility of using cardiovascular magnetic resonance surrogate markers to guide their use in future studies of lifestyle interventions.

I performed systematic reviews to identify 1) similarities and differences among leading primary prevention guidelines that address cardiovascular screening and risk assessment and 2) guideline recommendations on lifestyle advice and interventions to identify how e-coaching could be used and what advice to incorporate in e-coaching platforms.

I found modest but statistically significant improvements in both e-coaching and SOC groups to a similar level. Personalised e-coaching did not show additional benefit in a high-risk primary prevention cohort. It is feasible to use cardiovascular surrogate markers derived from cardiovascular magnetic resonance in lifestyle interventions studies. However, further studies correlating change in these markers with long-term outcomes are required.

Considerable discrepancies exist in the guidelines on risk on cardiovascular screening and risk assessment, with no consensus on optimum screening strategies or classification of high risk thus affecting treatment threshold. Guidelines did highlight the importance of lifestyle interventions in primary prevention and generally provided similar advice.

E-coaching should not be incorporated into current prevention programmes for high-risk populations unless the tools are improved and effectiveness is proven.

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Abbreviations list

ABA	Abdominal aorta
ACC	American College of Cardiology
AHA	American Heart Association
AI	Augmentation index
AMI	Acute myocardial infarction
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CFPWV	Carotid femoral PWV
CHD	Coronary heart disease
CI	Confidence interval
CIMT	Carotid intima media thickness
CMR	Cardiovascular magnetic resonance
CRP	C-reactive protein
CV	Cardiovascular
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
E-	Electronic
ECG	Electrocardiography
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EQ-5D-3L	EuroQol - 5 Dimensions - 3 level questionnaire
FRS	Framingham Risk Score
GP	General practice
HAPPY	Heart Attack Prevention Programme for You
HDL	High-density lipoprotein
hsCRP	High sensitivity
LDL	Low-density lipoprotein
LV	Left ventricular
LVH	Left ventricular hypertrophy
NHS	National Health Service

NICE	National Institute of Health and Clinical Excellence
NIHR	National Institute of Health and Research
NRI	Net reclassification index
PAR	Population attributable risk
PIS	Patient information sheet
PROCAM	PROspective CArdiovascular Munster
PWV	Pulse wave velocity
QRISK	UK validated Cardiovascular risk algorithm
QRISK2	UK validated Cardiovascular risk algorithm – version 2
RCT	Randomised controlled trial
RPAQ	Recent physical activity questionnaire
SCORE	Systematic Coronary Risk Evaluation
SF-36	Short form- 36 item questionnaire
SOC	Standard of care
SSFP	Steady state free procession
TAA	Ascending thoracic aorta
TDA	Descending thoracic aorta
UK	United Kingdom
USA	United States of America
USPSTF	United States Preventative Service Task Force

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Acknowledgements

There are many people who need thanking for their contributions to this thesis. Most important are the many patients who very generously consented to participate in this research.

I am indebted to my two supervisors, Professor Steffen Petersen and Dr Francesca Pugliese who provided invaluable professional support as well as personal friendship. They've given me the independence to explore different ideas and develop my research skills. They helped to make my research period a very positive experience.

I would like to thank all my colleagues in the Advanced Cardiovascular Imaging Unit, the William Harvey Heart Centre and Barts CMR unit who all contributed to my research in many different ways. In particular, I would like to thank Dr Armida Balawon and Achilles Radinos who provided valuable support that allowed successful completion of the study visits. I am grateful for all their hard work.

I would also like to thank Professor Myriam Hunink, Dr Bart Ferket, Dr Vinicius Bicalho and Claudia van Waardhuizen, who were my collaborators from the Erasmus Medical College in Rotterdam. They contributed to the successful completion of the systematic reviews of the guidelines on cardiovascular risk assessment and lifestyle advice that are presented in Chapter 5 and 6.

Lastly, very special thanks to my parents for their support and love and my wife and adorable children who have maintained patience with me during this period and allowed me to focus all my energies on the work in this thesis.

Chapter 1 – Cardiovascular risk reduction in primary prevention and role of electronic coaching

Preamble

In this chapter I outline impact of cardiovascular disease and the potential factors that are implicated in its development. I discuss the common factors that can be positively modified in order to reduce future risk and discuss the role that electronic coaching could play in this area. The influence of behavioural coaching is discussed with particular reference to the use of electronic media and highlighting the literature in this field and providing a rationale behind the HAPPY London study.

Background

Cardiovascular disease (CVD) remains a leading cause of death worldwide accounting for one-third of deaths.[1] Incidence and prevalence of CVD is expected to increase in the next decade due to escalations in obesity and an ageing population. The magnitude of this health care crisis calls for innovative health care measures to improve cardiovascular health. Changes in the body leading to cardiovascular complications usually develop over decades as a result of lifestyle, concomitant medical conditions and genetics. Changes in lifestyle and diet can significantly reduce the risk of developing CVD.

Although there has been a trend towards decreasing CVD mortality, the prevalence and thus the morbidity associated with this has increased in the UK in both men (7.1% to 9.1%) and women (5.2% to 6.3%) between 1994 and 2003. This increase may relate, in part, to the epidemic of obesity and diabetes[2,3]. The long latency period in the development of CVD provides an opportunity for early preventative intervention. Nine potentially modifiable risk factors accounted for over 90% of the population attributable risk (PAR) of a first myocardial infarction according to findings from the INTERHEART Study [4]. A Cochrane systematic review concluded that interventions using counselling and education aimed at behaviour change do not reduce mortality or clinical events in the general population but may be effective in reducing mortality in high risk populations [5]. There is growing

evidence that behaviour change using computer tailoring can be effective in changing lifestyle and risk factors [6,7]. Electronic media and particularly the use of the internet is a potential medium through which preventative strategies can be directed and may allow an efficient, easy to use and cost effective way to improve the health and wellbeing of many.

The aim of this thesis is to evaluate the effectiveness of e-coaching in the primary prevention of CVD in a high-risk population through lifestyle and risk factor modification.

Cardiovascular disease

CVD is an umbrella term for diseases that affect the heart and the circulatory system. Conditions that account for the majority of CVD include coronary heart disease (CHD), stroke, heart failure, atrial fibrillation and cardiomyopathies. CVD causes over 161,000 deaths in the UK annually accounting for over a quarter of all death. This has a direct impact not just on the patient, with alteration in the quality and length of life, but also a significant societal impact due to the costs of premature death, productivity loss, hospital treatments and increased prescriptions. It is estimated that the annual cost from the above is in the range of about £19 billion [8].

Myocardial infarction and its Impact

Myocardial infarction is usually an acute event that can have fatal consequences. A spontaneous or type 1 myocardial infarction is classified as an event that is related to an atherosclerotic plaque rupture, ulceration, fissuring, erosion or dissection that results in intraluminal thrombus in the coronary arteries [9]. This leads to reduced myocardial blood flow or distal platelet emboli resulting in myocyte necrosis. These patients most commonly have underlying CHD [9]. However, in about 5-20% the coronary artheroma may be non-obstructed or there may be no evidence of coronary artery disease at angiography [10].

Individuals that survive their myocardial infarction may be left with chronic debilitation due to heart failure, arrhythmias or angina. The British Heart Foundation has published statistics on the occurrence and impact of myocardial infarction and other related cardiovascular conditions in the UK. One in 3 people who have a heart attack will die before they even reach the hospital and it is estimated that every 7 minutes someone in the UK dies of a heart attack [8]. Myocardial infarction accounts for the most deaths from CHD with 103,000 myocardial infarctions in the UK every year. In England for example, an estimated 50,000 men and 32,000 women suffer a heart attack each year. All of these figures highlight the impact that this condition has at an individual and a national level.

Stroke

An estimated 152,000 strokes occur in the UK each year with about a 25% higher incidence in men compared to women. About 41,000 deaths in the UK are due to strokes each year. The long-term impact of a stroke is variable with some people making a full or almost full recovery at one end of the spectrum and others having profound debilitations and loss of independence. This has an adverse impact on quality of life and leads to further complications due to immobility, need for increased care and has financial implications on the individual and the health care system. The risk factors for CHD and thrombotic stroke are very similar and the main pathological pathway leading to these conditions are essentially the same, namely atherosclerosis.

Atherosclerosis

Atherosclerosis is the primary cause of coronary heart disease and stroke. Several different environmental and genetic factors have been identified as being important in the development of atherosclerosis[11]. Atherosclerosis is a progressive condition characterised by the accumulation of lipid and fibrous constituents in the large arteries. In the early lesion there is sub endothelial accumulation of 'foam cells' which are macrophages engorged with cholesterol. Evidence of early atherosclerosis can be seen during the first decade in humans. These early fatty steaks can then progress to more complex and obstructive lesions and may be

large enough to block the flow causing haemodynamic consequences to blood flow and thus symptoms of ischaemia. An acute occlusion, usually due to rupture or erosion of an atherosclerotic lesion followed by the formation of a thrombus can result in a myocardial infarction or stroke [11].

CHD results from a complex combination of genetic susceptibility and an unhealthy environment. The factors that have been associated with atherosclerosis can be divided up into those with a strong genetic component and those with a predominantly environmental component [11]. The factors that are known to have a strong genetic component include elevated levels of low-density lipoprotein (LDL) cholesterol, reduced levels of high-density lipoprotein (HDL) cholesterol, elevated blood pressure (BP) and diabetes mellitus. Factors that are mainly influenced by the environment include smoking, poor physical activity, high fat diet and infectious agents [11]. The factors mentioned above are all potentially modifiable but there are also some factors such that are not amenable to modification such as age, gender and an inherited risk that also have a bearing on development of atherosclerosis and thus CVD [12].

Risk factors for CVD

A number of risk factors for CVD have been identified. A small number of commonly occurring factors have thus been incorporated into mathematical risk calculators around the world in order to estimate an individual's future risk of developing CVD and with the aim of guiding individualised treatment, which may include lifestyle advice and pharmacotherapy. These factors were most widely described following the results from The Framingham Heart Study initially and popularised by other international studies including the INTERHEART study [4,13].

Primary prevention of CVD aims to reduce the first occurrence of a CVD event mainly in those who are healthy. Secondary prevention on the other hand aims to reduce the recurrence of CVD and its associated complication in someone who has established CVD.

The Framingham Heart Study

The Framingham Heart Study recruited its first volunteer in 1948 and has since grown into a large epidemiological study which now also includes the offspring of the original participants. This was a large landmark effort of its time and the origins were closely linked to the premature death of the president of the United States of America (USA), Franklin D Roosevelt. He died in 1945 from a stroke secondary to hypertensive heart disease. However, his treatment was extremely poor by current standards largely due to the very limited understanding of CVD, its risk factors and the need to treat conditions such as severe hypertension proactively [14].

The Framingham study investigators coined the term 'risk factors' and the factors that were identified to be linked to CVD helped physicians, other health care professionals and researchers to better understand CVD and further stimulated the interest in preventative cardiology [15]. The modifiable risk factors that were identified gave the opportunity to find candidates who may be asymptomatic but could be susceptible to future events. With the ability to predict and treat in advance there was a paradigm shift with the opinion that a coronary event should be regarded as a potential medical failure rather than the first indication for treatment [15].

The first CVD risk profile developed by the Framingham Heart Study was in 1977 and formed the basis of risk assessment in the USA and also in the UK. Only in the last decade has there been a move towards using other risk assessment tools in the UK, with the QRISK calculator taking over as the scoring system most validated for the UK [16].

INTERHEART Study

The INTERHEART study was a large standardised case control study of acute myocardial infarction (AMI) involving 52 countries around the world. It included 15,152 cases and 14,820 controls in the study and represented all of the inhabited continents of the world. Prior to this study our knowledge of the risk factors for

CHD were mainly derived from the developed nations such as the USA and Europe, but these developed countries only account for about 20% of the global burden of CHD. The remaining 80% of the burden was in the low and middle-income countries that represent a larger proportion of the world population [4].

The findings concluded that 9 modifiable risk factors accounted for about 90% of the PAR of AMI in men and 94% in women[4]. PAR refers to the proportion (or number) of cases that would not occur in a population if the factors were eliminated (e.g. how many lives would be saved if people did not smoke) . The 9 factors that were significantly related to AMI ($p<0.0001$ combined) were identified as smoking (with an odds ratio 2·87 for current vs. never, PAR 35·7% for current and former vs. never), raised ApoB/ApoA1 ratio (odds ratio 3·25 for top vs. lowest quintile, PAR 49·2% for top four quintiles vs. lowest quintile), psychosocial factors (odds ratio 2·67, PAR 32·5%), diabetes (odds ratio 2·37, PAR 9·9%), history of hypertension (odds ratio 1·91, PAR 17·9%), abdominal obesity (odds ratio 1·12 for top vs. lowest tertile and 1·62 for middle vs. lowest tertile, PAR 20·1% for top two tertiles vs. lowest tertile), regular alcohol consumption (odds ratio 0·91, PAR 6·7%), daily consumption of fruits and vegetables (odds ratio 0·70, PAR 13·7% for lack of daily consumption) and regular physical activity (odds ratio 0·86, PAR 12·2%). These associations were not limited to a particular gender, age or region of the world.

The understanding that abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, regular consumption of fruits, vegetables, and alcohol, and regular physical activity account for most of the risk of myocardial infarction worldwide have been key in public health efforts globally and in developing guidelines with the aim of reducing the burden of CVD including preventing a large proportion of premature AMI [17-21]. It is also evident that most if not all of these modifiable risk factors can be tackled with positive changes in lifestyle with some requiring the addition of complementary pharmacotherapy.

Smoking

The prevalence of smoking is between 20-25% in the different parts of the UK. England has the lowest average of 20% whereas in Scotland this is about 25%. Smoking has been linked as a strong risk factor for developing not just CVD but also other chronic conditions such as chronic obstructive pulmonary disease and cancers. About 100,000 people or more in the UK die from smoking related causes annually which includes an estimated 22,000 from CVD [8].

Passive smoking also increases the likelihood of fatal and not fatal AMI. In a meta-analysis assessing the impact of environmental tobacco smoke the pooled relative risk for nonfatal or fatal coronary events was 1.25 (95% confidence interval (CI) 1.17 -1.33) in non-smokers married to smokers compared to those whose spouses did not smoke [22]. At a cellular level environmental tobacco smoke has been shown to significantly increase platelet adhesion and endothelial damage of the arteries[23]. It can also lead to reduced exercise tolerance especially in those with CHD [24-26]. Although personal smoking history is included in commonly used CVD risk calculators passive smoking is not [16].

Hypertension

Hypertension is defined as a chronically elevated BP with clinic measured systolic reading of 140 mmHg or more, a diastolic BP of 90mmHg or more, or prescription pharmacological treatment for known hypertension. Hypertension occurs in over a quarter of the adults in the UK with only about half of this group actually receiving treatment. There is now a wide acceptance of using ambulatory measures of BP over 24 hours in helping to diagnose true hypertension [27,28].

Cholesterol

Over half of the adults in the UK also have a blood cholesterol level of 5 mmol/L or more. This has been considered the target level for some years but there has been a gradual trend to reduce this target with research suggesting the benefits of lower cholesterol levels, coinciding with a number of evidence based pharmacological

therapies, namely statins, becoming cheaper due to patent expiry [29]. Guidelines from the USA now advocate using statin therapy for individuals who have an estimated 10-year risk of CVD of 7.5% or above[30]. In the UK this was at a much higher level of 20% annual risk at which point treatment was deemed to be cost effective although the most recent National Institute of Health and Clinical Excellence (NICE) guidelines have also lowered their recommended threshold for considering initiation of pharmacological therapy to 10% [31].

Elevated serum cholesterol is recognised as a strong risk factor for CHD and associated increased mortality [32]. It has also been shown that lowering cholesterol levels can prevent CHD and have a positive impact on morbidity and mortality [33]. Treating asymptomatic individuals with hypercholesterolaemia is recognised as an important step in reducing the occurrence and the impact of CVD and is now widely recommended in guidelines. The treating the cholesterol is usually guided by an assessment of global cardiovascular risk using estimated risk calculators [17,34].

Obesity

Obesity is most commonly classified according to the body mass index (BMI) calculation. This is calculated using the height (in meters) and weight (in kilograms). The formula used is weight/height^2. A BMI of 25-30 kg/m^2 is considered as overweight and between 30-35 kg/m^2 as obese. The number of people categorised as obese has increased greatly on a global scale with an estimated 2.1 billion people now classified as overweight[35]. Nearly a quarter of the adults in the UK are obese and this is also becoming more apparent in childhood with a growing number of children also being overweight or obese.

Dietary Patterns

A sub-study of the INTERHEART study specifically looked at dietary patterns around the world and its association with AMI. They identified 3 major types of diets. They classified these as oriental, western and prudent. The oriental dietary pattern consisted of high intake of tofu, soya and other sauces and showed no

relationship with AMI. Higher levels of the prudent diet showed protective benefit and this consisted of patterns high in fruit and vegetables. The western pattern on the other hand showed a u-shaped association with AMI. When compared with the first quartile adjusted odds ratio for 2nd quartile was 0.87 but of the 3rd quartile this was odds ratio 1.12 and for the 4th quartile it was 1.35 (95% CI 1.21 to 1.42) [36]. The authors estimated that the adjusted AMI PAR of the dietary risk score was 30% when comparing the top 3 quartiles with the bottom quartile. The higher quartiles were representative of poorer dietary habits. The dietary factors considered were meat, salty snacks, fried foods, green leafy vegetables, cooked vegetables, fruits and other raw vegetables.

General principles of lifestyle and prevention

Primary prevention trials in the high risk adult population and secondary prevention trials in cardiovascular patients have shown that significant reductions in CVD risk can be obtained through lifestyle interventions [37,38]. Lifestyle intervention may be useful in general and when combined with additional motivational tools such as e-coaching, may work more effectively or maintain the enthusiasm. The INTERHEART study by Yusuf and colleagues suggested that the risk of myocardial infarction could be reduced by 80% from eating fruit and vegetables, being physically active, and avoiding smoking [4].

Atherosclerosis occurs over decades and although we can make predictions now on an individual's likelihood of developing CVD over 5 or 10 years this is based on population averages and it is very difficult to make exact predictions for the individual in question that you are managing. We now have a better understanding of the factors that can increase the chances of developing heart disease and have an armamentarium of tools that we can utilise to control these. Advances in pharmacology for hypertension, elevated cholesterol, the realisation of the harmful effects of smoking and the impact of lifestyle factors have been instrumental in helping to control common risk factors.

However, simple non-pharmacological approaches can have a large impact on reducing disease burden [39]. Physical activity for example has multiple benefits for

individuals physical as well as psychological health [40]. Almost everyone is able to do some form of physical activity despite physical limitations and if done in a sensible manner then few adverse side effects or complications can occur. Countries like the Netherlands have been proactive in allowing an environment that promotes a healthy behaviour including placing a large emphasis on physical activity in daily life. The provision of safe and abundant cycle lanes, for example, has allowed both adults and children to incorporate this form of physical activity in daily life [41]. Countries such as Australia have been proactive in the public health arena for smoking cessation. with smoking cessation programmes, a national recognition of the potential impact of legislation, such as plain packaging, and changing of the cultural norms in order to reduce the uptake and continuation of smoking [42].

Cardiovascular disease risk estimation

Framingham Risk Score

A number of risk scoring systems have been developed over the last few decades to try and identify asymptomatic patients that may be at high risk of developing their first CVD event in order that they may get timely advice on lifestyle optimisation and pharmacological therapy if required. The common modifiable lifestyle factors that have been targeted, as for example in the National Health Service (NHS) Health Check in the UK, include smoking cessation, increased physical activity and healthy diet. The main pharmacological aims have been towards lowering cholesterol and BP with the combined aim of trying to reduce long term CVD risk aiming to have a positive impact on quality of life and longevity[43].

Many guidelines have advocated estimation of risk for individuals as decision aids in management. This includes the Pooled Cohort Equation and the QRISK algorithm advocated in recent American and British guidelines [17,34]. The Framingham risk score (FRS) system was one of the first and widely used scoring systems in Western countries including the UK. There are a number of limitations with generalisability of the findings from the original study into other populations.

The original cohort was largely made up of a white, middle class population of Anglo-Saxon ancestry [13].

QRISK score

The UK CVD risk algorithm (QRISK) was developed using a prospective open cohort that utilises data routinely collected from general practice (GP) in the UK. A derivation cohort of 1.28 million patients between the ages of 35 to 74 years was used. This was based on data from 318 practices between January 1995 and April 2007 and in patients who were free of established CVD or diabetes. The QRISK score system has been validated and appears to perform better in the UK population compared to others [16]. The FRS and the Scottish risk algorithm (ASSIGN score) appeared to overestimate the number of people who would be classified as being high risk.

The QRISK calculator initially started by providing an estimate of the 10-year CVD risk and now includes the ability to calculate a lifetime risk. These risk estimates are individualised for smoking status, systolic BP, diabetes mellitus, total cholesterol to HDL ratio, BMI and a family history of premature coronary artery disease. Additional factors that are now considered in the newer QRISK calculators (i.e. QRISK2 and QRISK-lifetime), but were not included in the original Framingham scoring system or the original QRISK calculator are ethnicity, social deprivation (Townsend score, based on postal code), a diagnosis of atrial fibrillation, chronic kidney disease or rheumatoid arthritis. The 10-year and lifetime risk scores provide risk estimates, which include the occurrence of CHD, namely angina, myocardial infarction, transient ischaemic attack and stroke [44].

The NICE guidelines now recommend using risk calculators (particularly QRISK2) to help health care professionals target high-risk individuals in the population. The lower thresholds for initiating lipid modifying treatments advocated by the most recent UK and American guidelines have been the attention of much discussion [34]. Some of the reasons given for the change are that growing evidence regards the beneficial effects of statin therapy in lowering cardiovascular morbidity and

mortality along with the reduced cost of statins due to patent expiry, thus making it potentially more cost-effective to treat a larger population [31].

Concept of relative and lifetime risk

There has been a recent recognition in the area of risk estimation about the importance of relative or lifetime risk [34]. This is based on the observation that we may be underestimating risk in younger adults who would be categorised as having a low 10-year CVD risk but who are likely to accumulate this risk in the long run due to high levels of individual risk markers. New concepts to try and communicate this risk include 'heart age' in the JBS3 calculator, 'relative cardiovascular risk' in the European Society of Cardiology (ESC) Systematic Coronary Risk Evaluation (SCORE) system and lifetime risk as used in the QRISK lifetime score and the Pooled Estimate utilised in the 2013 American College of Cardiology (ACC)/AHA guidelines [17,19,34].

Impact of lifestyle on risk factors

Blood pressure

Exercise, weight loss and dietary approaches form part of the lifestyle interventions that have been shown to be useful for reducing BP. The Dietary Approaches to Stop Hypertension (DASH) diet was high in low fat dairy products and high in fibre from sources such as fruit and vegetables and showed reduction of 5.5 mmHg in systolic and 3 mmHg diastolic BP compared to a control group that consumed standard diet in the USA [45]. Exercise alone was shown to be associated with an average reduction of 3.3 mmHg systolic and 2 mmHg diastolic BP. Weight loss of about 8 kg was shown to reduce BP by about 8.5 mmHg systolic and 6.5 mmHg diastolic. A combined exercise and weight loss intervention in those who were overweight and hypertensive showed a reduction of 12.5 mmHg systolic and 7.9 mmHg diastolic [40].

Although the DASH diet has been shown to be successful in lowering levels of BP in feeding trials, in order to gain the maximum benefit, the individual need to

maintain good compliance in the longer term. A systematic review assessing the compliance to the diet based on 9 educational intervention studies that ran for at least 12 months showed that compliance rates were lower than reported in the original DASH trials [46]. The authors thus concluded that there is a need to investigate effective approaches to sustain the behaviour change with diets such as the DASH.

Cholesterol

Cholesterol lowering can be achieved by both lifestyle and pharmacological means. There have been a number of large clinical trials showing the benefits of statins in lowering not just the cholesterol levels but also hard cardiovascular end points in both primary and secondary prevention. Other cholesterol lowering medications do not have as robust an evidence base so far for event rate reduction and thus are predominantly used as second line therapy for individuals who do not tolerate statins [17].

Lifestyle modification can help to achieve target cholesterol levels as set out in various guidelines. The changes include dietary modification, weight reduction and increased physical activity with the aim of reducing cholesterol levels to below 5 mmol/L for total and less than 3 mmol/L for the LDL cholesterol [47]. In a recent review, dietary constituents such as green tea, soya protein, plant stenols and almonds have shown potential benefit in helping to reduce total and LDL cholesterol [47]. Due to the potential disutility of medication, people may prefer non-pharmacological means for reducing cholesterol[48]. However, compliance with lifestyle modification would need to be sustained in the long term to maintain its impact. This may not be possible due to factors such as poor patient motivation, financial cost, poor understanding and poorly perceived benefits of change [47].

Mediterranean diet

The Mediterranean diet consists of a high intake of olive oil, fruit, vegetables, nuts cereals and a moderate intake of white meat such as fish and poultry. This is combined with a relatively low intake of dairy products, red or processed meats,

and sweets. Wine is also usually taken with meals in moderation [49]. Observational cohort studies have shown an inverse association between adherence to a Mediterranean type diet and CVD events. An updated meta-analysis by Sofi et al showed that an increase in the adherence to a Mediterranean diet was associated with a significant lowering of overall mortality (relative risk =0.92, 95% CI 0.90 to 0.94) and cardiovascular incidence or mortality (relative risk = 0.90, 95% CI 0.87 to 0.93) [50]. It was also associated with significant reductions in cancer incidence and mortality and neurodegenerative disease. This has also been demonstrated in a secondary prevention CVD trial in 423 patients enrolled after their first myocardial infarction [51]. A significant difference was seen in 3 different composite end points with the main one being that of cardiac death and non-fatal myocardial infarction (14 events in Mediterranean type diet group vs. 44 in the prudent western type diet p=0.0001). A significant difference was also seen in the broad composite end points, which included the occurrence of unstable angina, stroke, heart failure, and pulmonary or peripheral embolism. This beneficial effect was maintained up to 4 years following the initial event.

In a large Spanish multicentre primary prevention trial, the Prevención con Dieta Mediterránea study, the investigators looked at the potential beneficial effects of the Mediterranean diet. Estruch et al conducted a large randomised controlled trial (RCT) with 3 treatment arms. The first 2 consisting of a Mediterranean diet with either extra virgin olive oil consumed daily (at least 4 table spoons) in one arm or mixed nuts in the other. The 3rd group were advised to take a low fat diet. The study was conducted over 6 years between 2003 and 2009 with a median follow up period of 4.8 years. The study was stopped early following the results of an interim analysis [52]. A total of 7447 participants considered to be high risk for CVD were enrolled and randomised into one of the 3 arms. All participants were considered high risk based on a history of diabetes or having at least three risk factors, which included smoking, hypertension, elevated LDL cholesterol, low HDL, a BMI of 25 kg/m^2 or more and a family history of premature coronary artery disease.

Both the Mediterranean diet arms supplemented with either extra virgin olive oil or nuts had a reduced incidence of the primary endpoint of combined major

cardiovascular events (myocardial infarction, stroke and death) The multivariable adjusted hazards ratio were 0.70 (CI 0.54 to 0.92) for the Mediterranean diet with extra virgin olive oil and 0.72 (CI 0.54 to 0.96) for the Mediterranean diet with nuts compared to the control group. A statistically significant lowering of stroke events in the 2 intervention arms mainly drove the benefit.

The study was sponsored by the Spanish government with the olive oil and nuts provided free of charge. Cost implications in real life settings may limit the adherence to this type of diet in the general population. Another limitation of the study was that for the first 3 years the control arm received less educational communication, such as individual and group educational session. The research group modified this in the study protocol about 3 years into the study.

Coaching

Coaching is a method of enhancing an individual's insight with the aim of shaping and encouraging behaviour that is seen to be optimal or desirable. The most widely known concept is in the field of sports but this can equally be utilised in several other contexts. Coaching is now widely used to try and improve healthy lifestyle behaviours. Weight loss, smoking cessation and physical activity programmes are a few examples of this [53]. In order for an individual to be able make a choice to lead a healthier lifestyle a few key elements are required. These include insight of the desired goal, knowledge and tools required to implement change, an environment that allows change and motivation to continue the action on a regular basis.

Guidelines on primary and secondary prevention of CVD advocate coaching in the form of cognitive behavioural therapy with specialist input for example with diet, physical activity and smoking cessation [19]. The progress that has been made in treating diseases such as myocardial infarction has greatly improved outcomes. This has been the result of improving emergency care such as thrombolysis in the past and percutaneous coronary intervention now. The contributions of pharmacological therapy and rehabilitation in the post infarction phase have also

been key in allowing individuals to return to their environment with improved quality of life and not just prolonging survival [54,55].

Modifiable risk factors and outcomes

Trials showing that reductions in total cholesterol in particular LDL component of cholesterol [29,56,57] BP and increased physical activity have led to reductions in mortality in patients with CHD although the application of these interventions are not always fully applied by health care providers [58].

Vale et al carried out a study on Coaching patients On Achieving Cardiovascular Health (COACH) in a multicentre RCT in patients who already had CHD. From 6 university teaching hospitals they randomised 792 participants to either usual care or usual care plus the COACH programme whereby additional personalised coaching was via telephone or mail to assess the primary end point of cholesterol change. The mean cholesterol reduction was significantly greater in the COACH group vs. the usual care (0.54 mmol/L vs. 0.18 mmol/L) at 6-month follow up. They suggested that coaching may have potential effectiveness in the other areas of chronic disease management [56].

Need for lifestyle and risk factor coaching

CVD events have an impact on morbidity and mortality. Many face adverse long-term consequences on quality of life and physical independence. The American Heart Association (AHA) and other bodies predict that the prevalence of CVD and the costs associated with it will increase substantially in the future. In the 2 decades from 2010 the real total direct medical costs of CVD are projected to triple to $818 billion from $272 billion. Indirect costs, due to loss of productivity, are estimated to increase by 61% by 2030 to $276 billion from $172 billion in 2010 [59].

Novel techniques in the primary prevention of CVD are required that are both clinically and cost-effective in the current climate of economic austerity. Use of the Internet and other electronic devices and tools have been suggested to offer a potential solution. However, to date robust evidence for this has been limited. The

expected increase in the incidence and prevalence of CVD, partly due to the rise in obesity and diabetes, is expected to have a heavy toll on health services. Responding through public health strategies and actively reducing risk factors has become widely accepted. This is evident from published medical guidelines for health care professionals; public health initiatives targeting children and government initiatives that are emphasising the important role that the food and drinks industry can play in helping people make a healthier choice[60].

Advantages of risk modification in high-risk groups

In a study of diabetic patients it was noted that intense modification of lifestyle and optimising pharmacological therapy had sustained beneficial effects on the rates of vascular complications and death when compared to conventional therapy[61]. The Cochrane reviews on multiple risk factor modification for primary prevention of CHD from 2006 and 2011 noted that interventions that use counselling and education aiming at behaviour change have not shown a reduction in total or CHD mortality or other clinical events in the general population but may be effective in reducing mortality in high risk patients with diabetes and hypertension. On the whole risk factor decline was modest but they were unable to perform pooled analysis due to heterogeneity between studies. The studies that looked at high-risk patients who had diabetes or hypertension seemed to show more positive results with potential for impact [5,62].

E-coaching

E-coaching is where coaching is delivered through the use of an electronic medium. The aims and goals are the same as regular coaching. E-coaching can be used as an alternative to regular coaching or as a complementary tool to emphasise and reinforce a message.

The use of electronic media globally now has a wide acceptance for personal and occupational use. Even in so-called developing countries there is wide availability of televisions, mobile phones and Internet. Since the advent of the Internet there has been an exponential increase in the availability of information. Search engines

on the Internet provide quick results, however, the quality of the information is not always guaranteed. Along with the rise in the availability of electronic media and information, there has also been a rise in obesity and diabetes. Although technology may be partly accountable for this, through more sedentary lifestyles, it can also be used as a source for facilitating access to potentially high quality information and motivation for behavioural change [63].

Computer tailoring for health behaviour change

Computer tailoring assesses the individual and selecting appropriate communication content using data-driven decision rules that rely on data input about that individual [6]. Computer tailoring involves "any combination of information or change strategies intended to reach one specific person, based on characteristics that are unique to that person, related to the outcome of interest and derived from an individual assessment" [64].

A meta-analysis looked at the effects of computer tailored interventions aiming to change health behaviours compared to non-tailored comparison groups. The computer tailoring included in this paper had to be primarily provided through electronic communication media and not live councillors. The control groups consisted of assessment only or minimal interventions including behavioural feedback, brochures or no intervention. The majority of the studies concentrated on one health behaviour, with less that studied 2 or more behaviours [6]. A search of publications between 1988 and 2009 identified 88 outcome studies. These studies included 4 health behaviours, namely smoking cessation, physical activity, healthy eating, and receiving regular mammography screening. They found clinically and statistically significant overall effects sizes in all 4 behaviours. They also noted that effect sizes decreased at further follow-up after the intervention was completed. Dynamic interventions had increased efficacy over those that were one off assessment. Study effects were similar between the different communication channels and were maintained when up to 3 behaviours were identified for intervention at the same time [6].

The authors concluded that computer tailored interventions have the potential for improving health behaviours. They suggested strategies that may help to optimise

the effectiveness of these techniques [6]. However, this work has been criticised for the lack of validity assessment and the reliability of the conclusions, due the heterogeneity between the 88 controlled studies reviewed. Also, the generalisability from this paper is limited due to the fact that 70% of the study participants were females and most of the studies were performed in the USA or Europe. The effect size was calculated using Hedges g method following extraction of outcome data. Overall a significantly greater effect was seen for tailored interventions compared to the control group with a small to medium effect seen with the interventions (g=0.17) but with evidence of statistically significant heterogeneity in the studies. All health behaviours were reported to have greater effects for the tailored interventions compared to the control groups. The largest effect was documented for dietary fat reduction (g=0.22, 95% CI 0.18 to 0.26 from 26 interventions) and also for other health behaviours including smoking cessation (g=0.16, 95% CI 0.12 to 0.19 from 32 interventions), physical activity (g=0.16, 95% CI 0.10 to 0.21 from 25 interventions) and fruit and vegetable intake (g=0.16, 95% CI 0.10 to 0.21 from 25 interventions) [6].

History of Computer and electronic interventions

The earliest computer tailored interventions used print material for communication. Recent advances in technology have resulted in the availability of this communication through computers, the Internet, mobile phone text messages and mobile phone applications. With the advent of wearable health gadgets this industry has seen a sharp increase in investment and potential capabilities[65]. Individuals can easily track their activity levels, estimated calorie consumption, sleep patterns and sedentary time. The ability to track serial changes and make this available to others has encouraged many to maintain healthier lifestyle and compete with others sharing the same platform as a means of further motivation.

In clinical trials of computer and electronic interventions there has been a wide variation in the strategies utilised. Differences exist in the type of intervention, the technology used, the number of contacts made, the number of factors attempted to modify, whether personalised or generic information was used and whether dynamic or static [6,7,66-68] approaches were chosen.

Health behaviour and pharmacotherapy

Health behaviour encompasses a broad group. This can be to do with lifestyle factors that are promoted such as healthy eating and maintaining good levels of physical activity but also involves avoidance of other harmful behaviours such as smoking, excess alcohol consumption. The prescription of medications has increased in the last century and is likely to increase further with the guidelines advocating earlier preventative interventions in the apparently healthy population [69,70]. It is also apparent that there is an aversion to taking medication in society unless it is likely to lead to a certain benefit [48]. Compliance for primary prevention CVD medications is as low as 50% after a median of 24 months of initiation [71].

For those who are likely to benefit from medications careful explanation of the benefits and harms of pharmacotherapy in addition to other positive encouragements is likely to lead to better understanding, empowerment and likely improved compliance of medications. A recent randomised controlled study using text messages showed significant improvement in medication compliance [72]. However, there was no difference noted between the 2 groups with regards to follow up BP or cholesterol levels. A number of potential reasons may account for this including the volunteering effect in those who take part in studies and thus potentially being healthier than the general population. Lifestyle modifications in addition to medical interventions have additive effects and thus should be encouraged together [17].

Mobile phones as a platform for information and coaching

Mobile phone use has soared in the past decade. They have become an attractive avenue for health care intervention delivery for a number of reasons: (1) People tend to carry their phone with them everywhere, (2) they are now widely adopted and in the USA for example more than 83% of the adult population have an active mobile phone. The availability and use of mobile phones has increased in developing countries and rural farmers in India for example can now take advantage of them in trying to boost their productivity, (3) people's attachment to

mobile phones, (4) advanced features on mobiles that allow context awareness and sensing which tracks phones based personal information such as activity levels and sleep patterns[73]. Mobile phones are now being used in conjunction with wearable tracking devices that allow seamless integration and instant feedback that allows progress recording and motivation.

Research on the clinical effectiveness of these recent advances are still limited, nevertheless, the market has now become a multimillion pound industry with intense competition and a race to bring about even better technology. The disadvantage of desktop computers and laptops is that they cannot be easily carried around as compared to mobile phones. Whereas a computer or laptop may be shared with others, mobile phones tend to have sole ownership thus making personalisation easier. People customise their phones to their settings and utilise them on a daily basis to call, text, schedule and carry out a large number of other activities. With easy access to the Internet along with other advanced facilities, mobiles are ideally placed to assist in health interventions both in the primary prevention and secondary prevention settings.

Pharmacies and GP surgeries have adopted text messaging reminders for appointments and prescription reminders to potentially help maximise on limited primary care appointment slots and encouraging compliance with medication for chronic diseases.

Examples of trials using e-coaching

E-coaching in familial hypercholesterolaemia

A randomised controlled study performed in the Netherlands used e-coaching in familial hypercholesterolaemia but found no significant improvement in CVD risk indicators using lifestyle intervention in people with familial hypercholesterolaemia as compared to usual care [74]. 340 adults with familial hypercholesterolaemia were recruited from a Dutch Cascade Screening programme and randomly assigned to either tailored web-based lifestyle advice and personal counselling or usual care. Intervention was personalised health

counselling intervention using a combination of computer generated tailored web advice and face-to-face counselling complemented with a telephone booster session. The goals of the intervention were (1) to improve awareness of the CVD risk though increased relevant knowledge cues to action and change in risk perception; (2) to improve motivation for healthy behaviour though increased knowledge and change in attitude, self-efficacy and social influence; (3) adopting and maintain a healthy lifestyle; (4) lower objective CVD measures. The group developed an individually tailored lifestyle intervention or CVD risk reduction in familial hypercholesterolaemia patients. They used the integrated model for exploring motivation and behavioural change (the I-change model dividing the process into awareness, motivation and action).

After 12 months they noted no significant difference in CVD risk indicators (namely lipids, systolic BP, glucose, BMI or waist circumference) between the groups. The cumulative long-term impact on CVD risk of small improvements in all indicators was not assessed. The authors cited the need for future studies to clarify this further. Some of the limitations of this study included that in this familial hypercholesterolaemia patients only less than half the intervention arm completed even 1 out the 6 of the advice modules. Their intervention was only using the computer programme and did not have addition email encouragements. The effectiveness of the intervention may be limited by the low usage of the intervention.

Computer-tailored coaching trials

The meta-analysis by Krebs et al found that computer-tailored interventions could have significant clinical impact on the rates of change in behavioural risk factors. Average point prevalence abstinence of smoking was 6% greater compared to the control group (20% in the computer tailored vs. 14% in the control) this effect would be comparable to between 4-8 in-person counselling sessions [75]. Adherence to physical activity recommendations was higher in the computer-tailored groups (43% vs. 34% in the comparison group). This is likely to have a significant impact as even in the UK only 39% of the population are thought to meet the recommended physical activity levels, from self-reported surveys [8].

Dynamic vs. static interventions

The dynamically tailored interventions appear to work better then static interventions [6]. Possible suggested reasons for this include the increased number of contacts for those in the dynamic group, as static tailoring with more than one contact showed similar effects (g=0.20 in dynamic vs. g=0.19 in static) [6]. However, over the follow up periods dynamic tailoring maintained the effect, whereas the static did not, thus suggesting that updating feedback to reflect the changes an individual makes may improve information relevance and the depth of processing information.

Communication channels

Interestingly there does not appear to be any significant difference between the types of communication channels used (e.g. print vs. computer tailoring). Only 3 studies were identified looking at automated phone delivery thus solid conclusions could not be drawn about this communication channel. The implication of this may be highly relevant. If electronic information is at least non-inferior and has the advantage of easier dissemination to a growing number of people with access to electronic media, it may have significant economic benefits being potentially more cost-effective than providing printed booklets or if face-to-face advise alone.

Number of behaviour changes implemented

Interventions on up to 3 behaviours simultaneously did not have a negative impact on the outcomes, in fact there were suggestions of a trend towards greater effect size with more behaviour change.

Limitations of published data

Limitations of meta-analysis in general is that they may over-represent studies with positive findings, as these are more likely to be submitted by researcher and published by journals compared to negative studies[76]. Also, although some of the

data show that clinically significant effects can be seen in the short term, there is little data available to see if the interventions are sustained in the long term. Cost effectiveness studies are limited in this field to guide how best to implement such strategies in clinical care.

Smoking cessation and computer and other electronic aids

A systematic review carried out by Chen et al. studied the effectiveness and cost effectiveness of internet, personal computer and other electronic aids to help adults to stop smoking [77]. In particular, they assessed the evidence for effectiveness of Internet sites, computer programmes, mobile telephone text messaging and other electronic aids for smoking cessation. They also looked at the cost-effectiveness of implementation of these tools in the NHS smoking cessation programmes and identified current gaps in research in this field. Findings suggested that the interventions are likely to be helpful in smoking cessation but the effect is small. Some forms of electronic intervention are likely to be cost-effective when delivered alongside brief advice or intense counselling.

Sixty relevant RCTs or quasi-RCTs were identified from a wide database search. Pooled estimates for both prolonged abstinence and point prevalence abstinence suggested that computer and other electronic aids increased the likelihood of smoking cession compared to self-help material or no intervention (relative risk 1.32 95% CI 1.21 to 1.45 and relative risk 1.14 with 95% CI 1.07 to 1.22, respectively). There was no difference seen in the effect when comparing smokers who were ready to quit to those who were not ready to quit but were being actively encouraged to stop. Cost-threshold analyses indicated that some form of electronic intervention were likely to be cost-effective when added to non-electronic behavioural support, but substantial uncertainty remained with regard to what the most effective type of electronic intervention was.

Text messaging

Txt2stop was a single blinded RCT by Free et al and used text messaging in smoking cessation using an automated mobile phone text-messaging

programme[78]. They enrolled 5800 smokers who expressed an intention to quit smoking and allocated them randomly to either receiving motivational text messages in addition to behavioural change support or a control group who received text messages that were unrelated to smoking cessation. At 6 months, biochemically verified continuous abstinence was significantly higher in the intervention group compared to the control (10.7% vs. 4.9% respectively, relative risk of 2.2 with 95% CI 1.8 – 2.68, $p<0.0001$). The text information was tailored to information that was provided at baseline by the participant and both groups could avail of additional smoking cessation support from other services that they chose. Despite the relatively low continuous abstinence rate in the intervention group it still represented an improvement. Missing data on participants that withdrew were accounted for using sensitivity analysis with multiple imputation techniques based on predictors of missing values. They subsequently reported on the cost effectiveness of the intervention and showed that personalised smoking cessation advice and support by mobile phone message would be cost saving to a health system [79].

Electronic tools assisting smoking cessation are now commonly used in New Zealand and the UK. In the UK the NHS Quit Smoking programme allows a number of different communication methods, including electronic, to be utilised free of charge for the general public [80]. This includes self-help material that is available at no cost through the post. They also have access to text messaging service for which they have consulted with the Txt2stop study group [78]. A number of other resources are also available, including desktop programmes (widgets), and there is also a smoking cessation application programme for smart phones that encourages setting a quit date and updates encouraging advice. A number of other initiatives including public health drive and the smoking ban legislation in public places in the UK along with plain packaging of cigarette boxes is likely to assist in reducing the detrimental societal impact of smoking.

Secondary prevention

A multicentre RCT enrolled 330 patients with established vascular disease with a 1-year follow up period. This trial investigated the potential benefits of an Internet

based, nurse led vascular risk factor management programme that promoted self-management on top of usual care. They found that the nurse led Internet based education programme in this group led to a greater reduction in the FRS compared to the control group that received usual care alone, although the effect was small [81]. They provided a personalised website with an overview and patients' risk factors status along with mail communication with the nurse practitioner through the website.

Potential benefits of e-coaching in health

The concept of using the Internet and other technologies to be able to provide services related to health from a distance hold promise. It could allow frequent contact between health professionals and the patient. This could also be cost effective on a large scale and could potentially function without over burdening existing health care facilities. Patients may feel empowered and motivated by understanding their health and being involved in the management process.

Internet programmes that target multiple lifestyle interventions have shown variable effectiveness but overall in the systematic review by Vegting et al of 9 trials in this category showed no additional benefit with respect to treatment of CVD risk factors [82]. The potential to be cost effective and reduction in visits to see the doctor have been identified as potential advantages even if it is not superior to usual care alone. However, cost effectiveness analyses are limited.

Internet access

According to the Office of National Statistics 2013 data, London has the highest rate of Internet users in the UK at 90%. Use of the Internet in the older population still remains high, with 80% of those between 55-64 having used the Internet at least once in the previous 3 months. Libraries provide free Internet access and there are many Internet cafes that allow easy access to those who may not have private Internet access. Added to this, acceptance and increased use in the general population and specifically the older generation, makes this an exciting tool with great potential. Additionally, in the last 5 years the use of smart phones has now made use of the Internet, even easier and thus not restricting access to home or work. In fact, over the last 3 years the London underground has expanded its wireless Internet access with availability even 40 metres below ground level.

HAPPY e-coaching

The Heart Attack Prevention Programme for You (HAPPY) programme initially used a method with generic lifestyle e-coaching as assessed in a Dutch population (n=1000) over 3 months. 141 of the participants with an intermediate to high cardiovascular risk were followed up over 12 months. This was an uncontrolled study that showed a relative reduction in cardiovascular risk of 13.8% based on the PROspective CArdiovascular Munster (PROCAM) study CVD risk score [83]. HAPPY incorporates the principles of computer e-coaching but now tailored to the individual users risk factors and suboptimal behaviour. It is not clear whether the Hawthorne may have had an impact on the outcomes. The Hawthorne effect refers to the tendency of people to work harder or perform better when they are being observed or part of an experiment. The change in behaviour may largely be due to the additional attention received rather than the medium through which it is delivered [84].

Chapter 2 – Cardiovascular surrogate markers

Preamble

In this chapter I discuss the use of non-invasive cardiovascular surrogate biomarkers particularly in the context of primary prevention of CVD. I discuss some of the technical aspects, strengths and weaknesses of using these biomarkers in order to justify their use in the HAPPY London study. The primary end point of CFPWV appears to best fulfil the criteria deemed necessary for use as a cardiovascular surrogate marker.

Background

Risk scores are useful for guiding prevention management. However, there is often a discrepancy between the predicted and the actual rates of events that occur. Biomarkers are tools that may help to further risk stratify patients.

A surrogate end point is a biomarker that may be a substitute for a clinical end point [85]. NICE states that a biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention"[86]. A surrogate endpoint in the form of a biomarker acts as a substitute for clinical endpoints. It is expected to predict the clinical benefit or harm based on scientific evidence. Changes in surrogates are often detected earlier than actual hard endpoints and thus may utilise less resources. This facilitates clinical trials allowing less time and lower cost and making trials more feasible to conduct. For a biomarker to be considered a surrogate for cardiovascular endpoints it must satisfy certain criteria. The AHA have outlined 6 required criteria for evaluation of a novel risk marker including proof of concept, prospective validation, incremental value, clinical utility, clinical outcomes and cost-effectiveness [86]. Other important factors that should also be considered are ease of measurement, methodological consensus, and reference values (Table 1) [87].

The potential role of peripheral non-invasive vascular biomarker for early vascular aging that could be used in primary and secondary CVD prevention were scrutinised by the ESC Working Group on Peripheral Circulation. Biomarkers that were deemed to fulfil most of the criteria required, and thus close to being considered clinical surrogate endpoints included carotid ultrasound, ankle-brachial index and carotid-femoral PWV [87]. Biomarkers that were deemed to fulfil some, but not all the criteria required included brachial-ankle pulse wave velocity (PWV), central haemodynamic/ wave reflections (pulse wave analysis) and C-reactive protein (CRP). Flow mediated dilatation, endothelial peripheral arterial tonometry, oxidised LDL and dysfunctional HDL were considered not to currently fulfil the essential criteria for surrogate endpoints. The group identified that a prospective study in which all vascular biomarkers are studied was lacking and considered that in selected cases more than one biomarker may be required for assessing an individual.

Table 1. Criteria for vascular biomarker to qualify as surrogate endpoints. Adapted from the ESC Working Group on Peripheral Circulation 2015[87]

1.Proof of concept	**Do levels differ between those with and without outcomes**
2.Prospective validation	Does it predict the development of future outcomes in a prospective cohort or nested case-control study?
3.Incremental value	Does provide incremental information above established standard risk markers?
4.Clinical utility	Does it change risk predicted enough to change recommended treatment?
5.Clinical outcomes	Does it improve clinical outcomes, particularly when tested in an RCT?
6.Cost-effective	Does it improve clinical outcome enough to justify the additional costs?
7.Ease of use	Ease of use allowing widespread application?
8.Methodological consensus	Is it measured uniformly in different labs and are the study results directly comparable?
9.Reference values	Are there published reference values?

Assessment of cardiovascular risk is important to facilitate accurate management decisions and for communication of future risk with the patient[88]. In order to make a tailored plan the risks and the benefits of the strategy must be considered in conjunction with the individual's baseline characteristics. A number of risk scores have been developed to allow this in clinical practice. The FRS in the past was

commonly used but has been superseded by other validated risk scoring systems such as the SCORE from the ESC and the QRISK for the UK[19,31] . Individuals can be classified into low, intermediate and high risk and this then helps determine the level of intervention that one could receive. Thresholds for determining the level of risk are often arbitrary and can change with time depending on resources and health care priorities.

There are a number of limitations to risk scores. Scoring systems vary in the data set used in its development, the population cohort included which in term affects is generalisability, the end points used and the duration of follow up considered [89]. Gaps exist between the calculated and the actual event rates, which can lead to under or over estimation. Risk scores need to be calibrated to the contemporary CVD event rates of the country where it is being implemented and need to take into account the changing population characteristics and the impact of other health interventions.

Some of the factors identified accounting for discrepancies include, but are not limited to extrapolation of the risk score to populations that are different from the original cohort used. The Framingham score, for example was originally based on a white Anglo-Saxon, predominantly male cohort from Framingham USA. This equation was previously used in the UK on people of South Asian origin. It subsequently became apparent that in this group the risk was often underestimated [16]. Other factors include the time delay between the observational studies being performed and when the scoring system is applied in clinical practice; the choice of the many risk factors that are included; and the strength of the endpoints used [34].

In the setting of primary prevention, a biomarker should be able to reflect the early morphological or functional changes before the disease conditions become clinically apparent. Thus providing a potential opportunity for early diagnosis and proactive treatment, thereby preventing the future occurrence of events.

Although a large number of biomarkers fulfil the first 2 criteria outlined above (proof of concept and prospective validation), they do not always add incremental

value, provide clinical utility or improve clinical outcomes. Even less is known about the cost-effectiveness of these markers. Most are easily measurable but only some currently have consensus on the methodology or reference values [87].

Arterial stiffness

In the developed world, myocardial infarction and stroke, the two leading causes of death are both consequences of atherosclerosis. Arterial stiffness occurs as a consequence of aging and arteriosclerosis rather than from atherosclerosis. Arteriosclerosis is a disease of the media and related to the normal or accelerated aging process. Atherosclerosis on the other had is principally a disease of the intima, affecting the vessel in a patchy manner. Loss of compliance results in an increased PWV as waves travel faster in rigid tubes. An elevated PWV is thus a hallmark of arteriosclerosis [87].

Arterial stiffness is recognised as an independent marker of cardiovascular risk beyond the established traditional risk factors [90-92]. It has predictive value for cardiovascular and all-cause mortality [93]. The aorta is the largest artery in humans and is one of the most commonly used vessel for assessment of arterial stiffness. Aortic stiffness is increased in a variety of common diseases, such as CHD and hypertension, and may be an early marker of atherosclerosis. Increased aortic stiffness has been shown to predict cardiovascular risk with hazards ratio 2.45 (95% CI 1.29 to 4.66) for CHD and hazards ratio 2.8 (95% CI 1.05 to 4.96) for stroke [94].

A large number of studies have assessed the pathophysiology of increased arterial stiffness and the conditions that are associated with it. The dominant effect appears to be related to aging and BP. Other factors include CVD risk factors, genetics, end-stage renal disease, and chronic inflammatory conditions. Arterial stiffness is thus considered a measure of the end organ damage on the arterial wall from these conditions. Numerous studies have validated the predictive value of arterial stiffness, and in particular for carotid-femoral PWV, including in essential hypertension [93,95], type 2 diabetes [96], end-stage renal disease [97], the elderly [98] and the general population [99]. Arterial stiffness is a robust predictor of all-cause

mortality suggesting that the role of arterial stiffness may extend beyond conditions that affect the cardiovascular system. It is also a robust predictor of cardiovascular mortality, non-fatal and fatal coronary end points and fatal stroke [92]. The predictive ability is higher in subjects with a higher baseline cardiovascular risk. Arterial stiffness can therefore be considered an intermediate end point for cardiovascular outcomes.

Changes in aortic stiffness can lead to an increase in the aortic pulse pressure and the afterload pressure encountered by the heart. This can have further pathophysiological consequences on the cardiovascular system such as promoting left ventricular hypertrophy (LVH)[100]. As arteries stiffen the heart is forced to work harder to allow the same stroke volume to be pumped against the increased resistance. This may lead to an increased time for the systolic phase of the cardiac cycle, which may have a consequent negative effect on coronary perfusion due to a reduction in the time available for the diastolic phase of the cardiac cycle. Aortic stiffness is thought to result in increased mortality due to its haemodynamic effect. Elastin fibres in the wall of the aorta normally bear the aortic stresses [101]. Mechanical fatigue and fragmentation of the elastin fibres within the aortic media is believed to result in dilatation of the proximal aorta and thus transfer of load to stiffer elements of the aortic wall such as collagen. Consequently, aortic wall stiffness causes a corresponding increase in the PWV, resulting in the premature arrival of the reflected pressure waves in late systole rather than diastole which augment the pressure [102].

Common ways of characterising arterial stiffness are with measurement of PWV (measured as m/s) and aortic distensibility (measured as 10^{-3} $mmHg^{-1}$) [90,103]. PWV is the propagation speed of the pressure along the artery and is calculated as the distance separating two locations divided by the transit time needed for the wave to cover this distance. Aortic distensibility describes the ability of the aorta to expand during systole and is calculated as the change in the cross sectional area of the artery divided by the local pulse pressure.

PWV in addition to pulse pressure increase mainly after the 5th decade of life and thus can be useful in this older age group to assess risk but also to look for

potential improvements following intervention. Augmentation index (AI) on the other hand appears to be a better marker of arterial stiffness in a population younger than 50 years of age [102].

Pulse wave velocity

PWV is the most validated method to non-invasively measure arterial stiffness. It is considered the gold standard index of aortic stiffness, as it is a relatively simple method with reported accuracy, good reproducibility and is an independent and strong predictor of adverse outcomes (nonfatal and fatal cardiovascular complications) over traditional risk factors in patients with disease and in the general population [99,104,105]. The most validated used technique and one that is most commonly practiced to date involves the assessment of pulse waves over a significant portion of the arterial tree such as the carotid-femoral PWV (CFPWV). Brachial ankle PWV is an alternative to CFPWV and involves putting inflation cuff around all 4 extremities. This technique is predominantly used in Japan with the potential advantage that measuring over a longer distance may provide additional information. However, it only meets some of the 9 essential criteria in order for it to be considered a clinical surrogate endpoint and is not recommended by guidelines [87].

Carotid-femoral pulse wave velocity

CFPWV met most of the 9 criteria outlined by the ESC working group for a vascular biomarker. It provides a long-term assessment of the impact of cardiovascular risk factors on the arteries. It is a validated non-invasive test, relatively easy to perform, relatively cheap and has been extensively validated. However, individual risk factors (such as BP) can fluctuate over a short period of time and may thus make it a less reliable measure of long–term outcome. The working group, however, concluded that it cannot yet be considered a surrogate endpoint and studies currently underway should help clarify this [87].

CFPWV measures the velocity of the pulse as it travels from the heart to the carotid and femoral artery. It assesses predominantly the elastic type arteries. This

remains the most commonly used non-invasive method for PWV assessment and is considered to be the "gold standard" [90].

CFPWV is normally measured using the "foot-to-foot" velocity method from a number of waveforms obtained from the common carotid and femoral artery using surface tonometry probes (**Figure 1**). The time delay also known as the transit time, is measured between the foot of the two waveforms measured simultaneously [104]. The foot is defined as the end of diastole, when the steep rise of the wave begins. The transit time is the time taken for the foot of the wave to travel over a known distance. A variety of waveforms including pressure, distension and flow can be used for the assessment [104,106]. The distance is measured as the skin distance between the two sites being recorded. PWV is derived from distance/ transit time and is measured in meters per second (m/s).

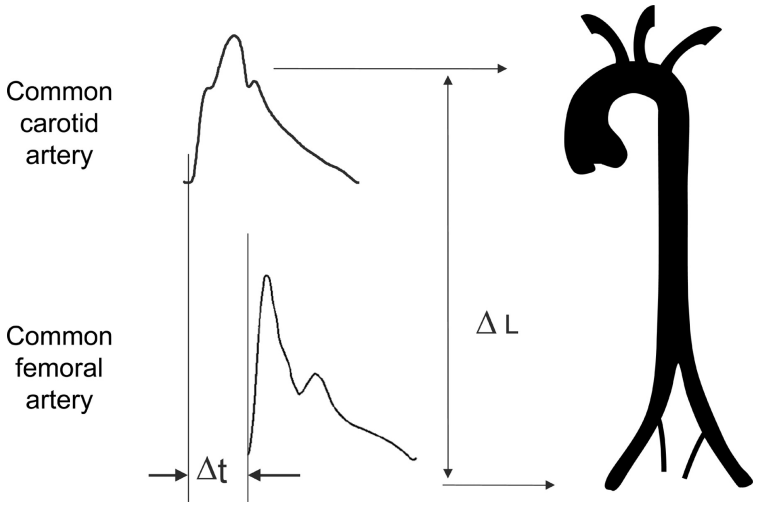


Figure 1. Measurement of carotid-femoral PWV with foot-to-foot method using the equation distance (ΔL)/ transit time (Δt). Laurent S, Cockcroft J, Van Bortel L et al, Expert consensus document on arterial stiffness: methodological issues and clinical applications, Eur Heart J. 2006; 27(21): 2588-605, by permission of the European Society of Cardiology[90].

In a meta-analysis of 16 studies looking at the predictive ability of PWV for CVD events, CVD events increased by 30% for every 1 standard deviation increase in CFPWV with a 95% CI of 1.18 – 1.43 even after adjustment for traditional cardiovascular risk factors [107]. The authors suggested that PWV had potential to

enable better identification of high-risk populations that might benefit from more aggressive CVD risk factor management. CFPWV has also demonstrated added value over and above global risk scoring systems that take multiple risk factor interactions into account, such as the SCORE from the ESC [108].

Meta-analyses have demonstrated a good net reclassification index (NRI) of CFPWV in patients at intermediate risk. In an individual data meta-analysis of 17,635 individuals, the 5 year overall NRI for CHD was 14.8% and 19.2% for stroke [107]. To date there have been no randomised controlled studies assessing the potential of CFPWV as a target for therapy and if such a strategy is likely to lead to improved outcomes [87]. One study in end–stage renal disease patients showed improved outcomes for those with a lowering of their arterial stiffness [109].

Cost-effectiveness studies for the use of arterial stiffness in clinical practice are lacking. It is thought that the there is a potential for cost saving from the high reclassification index and the relatively low cost for an individual patient, particularly if performed on a large scale [87].

Reference values for healthy subjects have been published based on 1455 individuals and also in patients with cardiovascular risk factors[110]. The mean values in the normal group showed a trend to wards an increase in PWV by increasing age (grouped in decades). An expert consensus paper on the measurement of CFPWV is available and generally accurate measures are possible after a relatively short operator training period [87].

The European Society of Hypertension (ESH)/ ESC guideline on the management of hypertension advocates the use of CFPWV in clinical practice. Initially a threshold of 12 m/s was suggested to determine significant pathology of aortic function in middle-aged hypertensive subjects [111]. It should be noted that the relationship between CFPWV and cardiovascular outcomes is a continuous one and the cut-off was based on expert consensus trying to simplify its use in guiding management in clinical practice. In a more recent consensus paper the cut-off has been lowered to 10 m/s to try and normalise the PWV to the arterial pathway [106].

The initial threshold was based on the use of the full direct distance from the carotid artery to the femoral artery.

Central Haemodynamics and wave reflections

Central haemodynamic outputs are either central BP parameters and its derivatives (including central systolic BP, pulse pressure and augmented pressure) or measures that quantify wave reflections (such as AI, wave intensity analysis, forward and backward waves). Although invasive measures provide accurate indices of central pressures and wave reflection, there are associated risks and thus non-invasive alternatives are preferentially used in clinical and some research areas [112].

LV afterload is dependent on properties of the steady state (peripheral circulation and the aortic valve) and the pulsatile components (elasticity of the large arteries including the aorta). A number of different models have allowed quantification of mechanics of the systemic circulation. A commonly accepted model and thought to be the most realistic describes the pressure and flow waves as being generated with every heartbeat. These are then propagated to the peripheral system and from there they are reflected back towards the heart. The reasons for the backward reflection include stiffness gradients, the presence of bifurcations and the abrupt diameter gradient in the arteriole. The reflected waves then merge with the anterograde wave and thus amplify it [113]. This may partly be the explanation for why peripheral BP is generally higher than the central BP to varying degrees, called the 'amplification phenomenon'. Central BPs are the pressures that the vital organs such as the heart, kidneys and brain are exposed to and thus thought to be more relevant indices compared to peripheral BP [113].

With aging, largely due to the increased aortic stiffness, the arrival of the reflected wave in the ascending aorta shifts into the systolic phase due to earlier return of the wave thus resulting in a change in the shape of the wave. The amplitude of the reflected pressure waves increases further with vasoconstriction. These two processes lead to increased central systolic pressure, lowering of diastolic pressure and the degeneration of the elastic component of the arterial wall.

Increased central systolic pressure is likely to lead to increased oxygen consumption with increased cardiac afterload and lower diastolic pressure leading to decreased myocardial perfusion pressure. The net effect leads towards myocardial ischaemia and an impairment of LV function, mainly affecting the diastolic function [87]. Central haemodynamic measures can also be particularly useful in young individuals with isolated elevation of systolic BP. It can help to identify those who do not have associated increased central pressures and thus avoiding the need for further investigations or pharmacotherapy [114].

The classical pulse wave analysis involves assessment of the pressure waveform alone from the radial, brachial or carotid artery (Figure 2). A transfer function in the form of a mathematical algorithm, in addition to calibration to a non–invasively measured pressure provides central waveform parameters including aortic pressure, augmentation pressure and AI. Augmentation pressure is a measure of the enhancement of the central aortic pressure by the reflected pulse wave and AI represents the ratio of augmentation pressure to the pulse pressure [115].

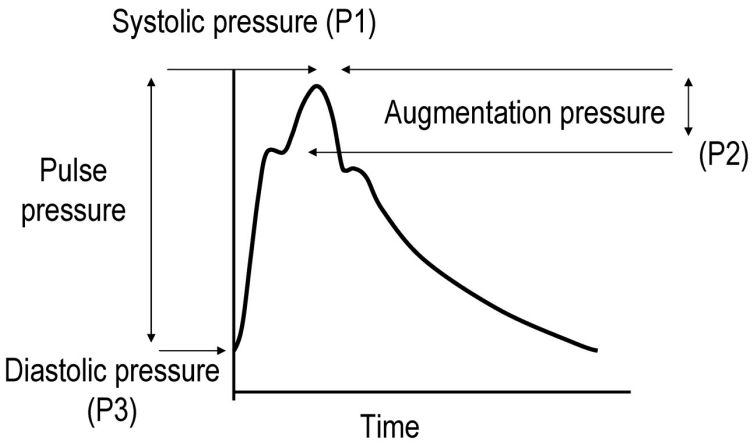


Figure 2. Carotid pressure waveform as recorded by applanation tonometry. The height of the late systolic peak (P1) above the inflection (P2) defines the augmentation pressure, and the ratio of augmentation pressure to pulse pressure defines the AI (in percent). Laurent S, Cockcroft J, Van Bortel L et al, Expert consensus document on arterial stiffness: methodological issues and clinical applications, Eur Heart J. 2006; 27(21): 2588-605, by permission of the European Society of Cardiology[90]

In a meta-analysis of 11 longitudinal studies including 5648 individuals, central systolic BP, central pulse pressure and AI were independent predictors of

cardiovascular events. Central AI was also noted to be an independent predictor of all-cause mortality [112]. AI predicted clinical events independently of peripheral pressures, while central PP had a marginally but not significantly (P = 0.057) better predictive ability when compared with peripheral pulse pressure.

Trials of antihypertensive medications have shown improvements in intermediate endpoints such as LV mass, after a reduction of wave reflections and central pressure [116]. The change in LV mass was linked to central and not brachial BP. The Conduit Artery Functional Evaluation (CAFÉ) study showed that an improvement in the wave reflection leads to a reduction in cardiovascular events. In this study calcium channel blockers showed similar reductions in peripheral systolic BP compared to a beta-blockers but was more effective at lowering the central systolic BP and reduced subsequent cardiovascular events [117].

A consensus statement on the use of central BP measurements and antihypertensive medication use along with reference values for these parameters have been published [118]. The ESH/ESC guidelines for the management of hypertension suggest that AI and central BP may be helpful when assessing young patients with isolated elevations in systolic BP [111].

One of the disadvantages is that peripheral pressure is required for calibration of the central pressure. Central pressures cannot thus be derived by itself without peripheral pressure measurement. Also central BP, central PP, and AI are dependent on the speed of wave travel, the amplitude of reflected wave, the reflectance point, and the pattern and duration of ventricular ejection, especially with respect to change in heart rate and ventricular contractility[119]. Aortic PWV on the other hand is the speed of wave travel. AI is much more sensitive to the effects of heart rate and arrhythmia than aortic PWV, particularly if a number of beats are measured and averaged. PWV is derived from simultaneously measuring the same beat from both the carotid and femoral artery and should be less affected[120].

C-reactive protein

CRP is a circulating biomarker that can be measured from a serum sample. It is a marker of systemic inflammation and is elevated as a result of vascular disease [121]. It is related to the vascular wall biology and a large number of studies have

supported its use for risk assessment. High sensitivity (hsCRP) levels correlate with traditional risk factors including BMI, systolic BP, lipids and fibrinogen levels. In a meta-analysis of 160,309 subjects the risk ratio for CHD was 1.37 for every SD increase in the log (e) CRP concentration (a 3–fold increase) even after adjusting for conventional risk factors including age and gender. The NRI was modest at 1.52% [122].

The Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvostatin (JUPITER) study used elevated hsCRP as an indication for statin therapy, despite absence of dyslipidaemia, resulting in beneficial cardiovascular outcomes. This study reinforced the relationship between inflammation and cardiovascular outcomes. The trial did, however, receive criticism. A cut-off value of 2mg/L was used in the study and has been proposed for cardiovascular risk stratification. However, a single threshold value may not be ideal and is somewhat arbitrary.

The ESC guidelines advocate its use in those at intermediate cardiovascular risk only. The most recent 2013 ACC/AHA advocate its use in only a limited group where treatment decision is uncertain and is likely to be modified following the test results [19]. Currently it has very limited use in clinical practice for CVD risk assessment in the general population.

HsCRP levels can transiently increase due to common inflammatory processes such as viral upper respiratory infections. It should thus be measured in a well state or following full recovery from an acute illness. For this reason, it lacks specificity for CVD.

Cardiovascular magnetic resonance imaging

Cardiovascular magnetic resonance (CMR) has had a rapid development since the beginning of the century. It is a non-invasive test that provides unparalleled image quality. CMR also allows modelling of the LV without geometric assumptions or dependence on acoustic windows and thereby showing better accuracy and reproducibility compared to echocardiography[123]. CMR is the current gold standard for LV function and mass assessment. CMR in comparison to echo has been shown to require fewer participants to assess change in cardiac structure and function due to its high reproducibility [124]. This makes CMR more likely to be cost-

effective compared to echocardiography. Other useful markers that can be obtained include PWV and aortic distensibility [125]. These measures have been utilised in a number of studies assessing the use of antihypertensive medications but to a limited extent to assess the effects of predominantly lifestyle modifications [126,127].

The general disadvantages of CMR include the longer image acquisition time. Presence of cardiac devices, such as pacemakers and defibrillators, are current contraindications to CMR scanning. MRI conditional devices are now coming onto the market but have specific conditions that need to be fulfilled before, during and after scanning. There is also concern about the rare but serious complication of nephrogenic systemic fibrosis that has been reported due to use of gadolinium based contrast media in patients with end stage renal disease or those on dialysis. Although, contrast is not actually required for assessment of arterial stiffness by CMR, it may limit the comprehensive study of the cardiovascular system. Up to 10% of the general population may be unable to tolerate a scan due to severe claustrophobia [128] . It has recently been demonstrated that gadolinium can accumulate in the brain after its administration even in patients with normal renal function. The clinical significance of this finding is not yet known with no direct links to the development of dementia [129,130] .

Aortic distensibility using cardiovascular magnetic resonance imaging

Aortic distensibility can be assessed using CMR steady state free procession (SSFP) cine sequences using electrocardiogrphy (ECG) gating. The change in the cross sectional area of the aorta can be accurately measured using manual or semi-automated aortic contouring and area measurement. Velocity encoded CMR with phase contrast sequences allows assessment of the blood flow velocity and the ability to study the propagation of the aortic systolic flow wave. With sufficient spatial and temporal resolution this is reproducible and accurate [125].

CMR has been validated for the assessment of aortic PWV and distensibility [131-133]. It allows assessment of aortic structure and function with direct high-resolution imaging with measures of aortic area change, aortic strain (relative change in area, in %), aortic distensibility ($10^{-3}mmHg^{-1)}$ and aortic PWV 9 m/s. Greater accuracy is

possible using direct aortic path length, that is required to measure the aortic distance for PWV, rather than surface lengths that are used for conventional applanation or oscillometric devices (e.g. Vicorder). This avoids the potential error of underestimating the aortic length due to tortuosity and variations in the surface landmarks that different studies may use [128].

Redheuil et al compared several non-invasive techniques used for the assessment of the elastic properties of the aorta and reported aortic distensibilities with CMR using central pressures. Distensibility of the ascending aorta correlated strongly with aortic arch CMR-derived PWV ($r = 0.73$, $p = 0.0001$). Both of these indices were more strongly and specifically related to aging than the indices derived from applanation tonometry (CFPWV, AI) or carotid distensibility[133].

Full 3-dimensional visualisation of the aorta permits reproducible aortic distensibility measurements [128]. CMR allows this to be quantified as change in 2-dimensional vessel circumference or area rather than 1-dimension vessel diameter obtained by echocardiography. This is largely possible, as the imaging plane can be placed directly perpendicular to the vessel. Regional stiffness through assessment of the local distensibility and the regional PWV can be measured at different locations of the arterial tree without the limitation of incomplete visualisation of the aorta, particularly involving the aortic arch. CMR is very versatile and also allows other measurements such as aortic wall strain, deformation, LV function and LV mass to be taken during one scan [125,134].

LV mass

LVH is a pathological increase in the left ventricular (LV) mass that independently predicts adverse outcomes in a variety of cohorts [135, 136,137]. An increase in LV mass predicts cardiovascular complications associated with hypertension [124]. In patients with essential hypertension and ECG criteria for LVH a reduction in LV mass, as measured by echocardiography, during antihypertensive treatment is associated with lower rates of clinical endpoints, this is independent or in addition to the effects of actual BP lowering or the treatment modality [138].

These findings suggest that LV mass reduction during treatment may provide additional information and may act as a surrogate marker for disease control and for prognostication. This theory has been seen in some ECG studies but data from echo or CMR are limited but do support the association of LVH regression with lower cardiovascular endpoints [139,140]. LVH on echo is associated with increased incidence of heart failure, ventricular arrhythmia, death following acute myocardial infarction, reduced LV ejection fraction, sudden cardiac death and stroke [141]. Previous outcome studies have shown that a ~5g/m^2 higher indexed LV mass can be predictive of a 7-20% increase in CVD morbidity and mortality [142,143]. In studies conducted in morbidly obese patients undergoing bariatric surgery significant changes in LV mass have been shown [144].

The influence of long-term treatment on preventing increase in LV mass has had limited study outside the context of clinical trials. Several trials have demonstrated that LV mass regresses in the short term with antihypertensive treatment as seen in a meta-analysis of 80 RCTs in essential hypertension (n=3767) with 146 active treatment arms and 17 placebo arms (n=346) [145]. Most of the studies had a mean follow-up period of between 25 to 35 weeks. There was a difference in LV mass regression based on class of antihypertensive treatment. Indexed LV mass decreased by 13% with angiotensin II receptor antagonists (95% CI- 8% to 18%), 11% with calcium channel blockers (95% CI 9% to 13%), 10% with angiotensin converting enzyme inhibitors (95% CI 8% to 12%), 8% with diuretics (95% CI 5% to 10%), and by 6% with beta-blockers (95% CI 3% to 8%). Although differences were noted the authors concluded that it still remained to be determined whether a greater reduction in LV mass resulted in better clinical outcomes.

CMR is considered the current gold standard for LV mass assessment[146]. Echo can also provide this information with improved spatial resolution, advanced analysis tools and ability to obtain multi-slice short axis views with 3-dimensional echo. CMR has an advantage over echo in that it does not suffer from poor windows in obese patients, those with hyper-inflated lungs and is less operator dependent and more robust in reproducibility and assessing change as compared to echo [123].

Aortic stiffness: Pulse wave velocity

PWV can be measured using CMR and had been validated for reliable non- invasive assessment of aortic -and correlates well with other non-CMR cuff methods [131]. An advantage over oscillometric methods is that there is no assumption/ error in measuring the aortic distance which can be measured directly using aortic slices [131,132]. To assess PWV by CMR, flows need to be acquired from at least 2 aortic levels to assess the distance between these points. CMR allows great flexibility in selection of the levels of the aorta allowing both regional and global measures.

Aortic stiffness: Aortic distensibility

The elasticity of the aorta reduces with stiffening and thus improvements in aortic distensibility may be used as objective evidence of functional improvement. Factors that lead to reduced distensibility include smoking, hypertension and obesity, which are known risk factors for CVD [147]. Aortic distensibility, particularly at the level of the proximal aorta, is an independent predictor of all-cause mortality and incidence of cardiovascular events[148]. Aortic distensibility can be assessed at multiple sites of the aorta and CMR is one of the few imaging modalities that allow functional assessment of the aorta in such a flexible way. Echo provides only limited thoracic aortic views with certain blind spots.

Carotid intima media thickness

An early part of the atherosclerotic process involves the infiltration of the sub intimal layer of the arterial wall by lipids and inflammatory cells. A thick intima-media serves as a proxy for atherosclerosis elsewhere in the body [149]. The presence of plaque is seen as a more severe form of the atherosclerotic process. They can both be assessed at the same ultrasound examination and provide complementary information. Carotid ultrasound allows the assessment of both carotid intima media thickness (CIMT) and carotid plaque. The procedure is relatively easy to perform with training and can be done with the widely available ultrasound scanners in clinical practice.

Risk prediction should be based on assessment of the carotid arteries for detection of plaque along the carotid artery and the measurement of the CIMT at the site of the common carotid artery [150]. This site was found to have highest accuracy of measurement of CIMT, including the lowest inter and intra-observer variability [151]. The preferred method suggests that the reading should be performed using semi-automated software, over a segment of artery covering 1cm. With better temporal and spatial resolution the echo tracking technique is an alternative method. The reproducibility of both techniques appears to be similar in patients with increased risk or atherosclerotic disease [152]. Increased CIMT is generally agreed as being a measure above the 75th percentile value for a reference population. The ESC has set a value of above 0.9mm in recent guidelines as a marker of high risk [153]. However, this simple cut off value may lead to misclassification where the reference population values differ.

Prospective cohort studies have documented the predictive value of CIMT for future cardiovascular events. A meta-analysis of 36,984 subjects showed an increased risk for future cardiovascular events of 16% for every 0.1 mm difference in the baseline CIMT [154]. However, another larger meta-analysis of 45,828 subjects from 14 cohort studies showed that common CIMT did not add significant information to the FRS with regards to the first myocardial infarction or stroke event [155]. Incremental value of CIMT over the 10-year FRS was assessed in a meta-analysis involving the general population. Fourteen population-based studies involving 45,828 subjects over a median follow-up of 11 years were included. The NRI to the FRS with addition of common CIMT was small (0.8%; 95% CI 01%-1.6%). In those at intermediate risk, the NRI was slightly higher but with no difference between men and women [155].

Although CIMT has been used in randomised studies as an intermediate end point of novel drugs it has been shown that CIMT changes do not have a prognostic implication for future risk prediction as shown in a meta-analysis of 36,984 subjects where CIMT progression was not linked to future cardiovascular outcome [154]. Guidelines on primary prevention now recommend against the use of CIMT in the general population [19,34].

Carotid plaque

Carotid plaque is thought to represent a later stage of the atherosclerotic process or possibly a different phenotype compared to CIMT. Total plaque volume is the most commonly measured parameter with good inter- and intra-observer agreement of >90% [156]. 3D techniques may offer a better estimate but robust studies to assess this are pending. In a clinical setting measures that can be easily obtained and show good reproducibility include (1) the presence of absence of carotid plaque, (2) the number of plaques, (3) and descriptions such as plaque maximum thickness [157]. Lipid lowering medication have shown to lead to reduction in plaque volume to a small extent [158].

Ultrasound assessment of carotid plaque appears to have a higher diagnostic accuracy for the prediction of future coronary artery disease, compared to CIMT measurement [159]. The presence of carotid plaque predicts cardiovascular mortality independent of the risk prediction using the SCORE algorithm advocated by the ESC. Presence of plaque increases the risk of cardiovascular mortality by 2 fold in the intermediate risk and 4 fold in the low risk groups [108,160]. The Multi Ethnic Study of Atherosclerosis (MESA) study showed that plaque measures improved risk prediction and that increasing risk was associated with a greater number of plaques but this was not seen with increasing CIMT [157,161].

Carotid ultrasound driven therapy leading to improved outcomes has not been established yet [87]. Higher values of CIMT or presence of plaque are considered as markers of end organ involvement and may be used by clinicians to be more aggressive with risk factor intervention. However, up to now there have been no studies that support this strategy. Informing patients of their results does not seem to have a consistent impact on motivation for change [162,163].

Carotid plaque meet most of the 9 essential criteria outlined by the ESC working group on Peripheral Circulation, whereas CIMT only meets some of them [87].

The most recent ACC/AHA guidelines have downgraded CIMT and recommend against its use in the asymptomatic adults for prediction of the first atherosclerotic CVD event. Plaque assessment was not considered for the purpose of this guideline

review [34]. The ESC/ESH guideline for the management of arterial hypertension have recommended ultrasound scanning for CIMT and plaque detection in management of hypertensive patient [111]. The ESC guideline on CVD prevention previously gave a recommendation that it should be considered in intermediate risk individuals [153]. However, the updated version of this guideline published in 2016 now also recommended against its use [19]. The guideline group raised concern about CIMT assessment including the lack of standardisation regarding the definition and measurement of IMT, high variability in measures and low intra-observer reproducibility. This change in the recommendations against the use of CIMT has been driven by the most recent meta-analysis that failed to demonstrate added value of CIMT compared to the FRS in predicting future CVD, even in the intermediate risk group where it was previously felt to be potentially useful [155].

Effects of lifestyle on surrogate biomarkers

Lifestyle modification can have a beneficial effect on vascular biomarkers. For example weight reduction lowers CRP, CIMT, wave reflections and arterial stiffness [164-166]. This effect is more pronounced when weight reduction is combined with increased physical activity [167]. Endurance exercise improves central haemodynamics, whereas resistance training has a detrimental effect on arterial stiffness[168]. Beneficial effects on central haemodynamics have been seen after stopping smoking [169].

Certain foods have also been shown to reduce aortic stiffness, wave reflection and central systolic BP such as cocoa[170]. Caffeine on the other hand increases central BP as well as arterial stiffness in healthy individual and those with hypertension[171]. The rise in CFPWV appear to reach a peak one hour after consumption and them progressively decreasing thereafter towards baseline. The effect of caffeine appears to last for than 3 hours[171]. For this reason, caffeine should be avoided prior to measurement of central haemodynamic measures, particularly when performing serial measures assessing for change.

Chapter 3 - Methods

Preamble

In this chapter I outline the methods for the HAPPY London study including the experimental design and assessments performed as part of the study. The interventions are explained with descriptions of the advice and resources available to the e-coaching group and the standard of care group.

The HAPPY London Study

Purpose

The primary aim of this study is to assess the clinical effectiveness of individualised, continuous e-coaching to support a healthier lifestyle as a primary prevention tool to reduce the cardiovascular risk in asymptomatic individuals with intermediate to high 10-year cardiovascular risk.

Our primary hypothesis was that computer tailored e-coaching in addition to standard care would lead to a greater reduction in PWV compared to standard care alone.

The HAPPY London study was conducted as a RCT comparing the use of tailored e-coaching in addition to the SOC vs. SOC alone. Standard of care was defined as the care that would be offered by the NHS Health Check programme or through the primary care services. I used a range of established and novel cardiovascular markers to determine the clinical efficacy and aimed to conduct a cost effectiveness analysis of e-coaching and gain pathophysiological insight into how lifestyle modifications affect the cardiovascular system. These measures included CMR, aortic stiffness parameters, vascular ultrasound and other biomarkers of cardiovascular disease risk.

Primary outcome

The primary outcome measure was the change in aortic stiffness as measured by PWV using a Vicorder device.

Secondary outcomes

- CMR change in LV mass index and aortic distensibility
- Change in the CIMT using ultrasound (CardioHealth system, Panasonic)
- Change in the Framingham and QRISK2 score
- Change in physical activity levels, change in diet, smoking, alcohol and other factors through questionnaires.

Experimental design

The HAPPY London study is a single centre, randomised controlled parallel arm clinical trial. Participants were enrolled and completed 6-month follow up between July 2013 and May 2015.

HAPPY London provided personalised feedback to the e-coaching group participants throughout the 6-month period and incorporated serial surveys and questionnaires, which allowed dynamic feedback during the study period. In addition to these tailored questionnaires, participants completed other questionnaires at baseline, 3 months and 6 months (recent physical activity questionnaire (RPAQ), the short form – 36 item questionnaire (SF-36), EuroQol- 5 Dimension- 3 Level questionnaire (EQ-5D-3L, developed by the EuroQol group as a standardised measure of health status), and Big five (to capture personality traits, time-preferences and risk perception using the questionnaire devised by Professor Thomas Dohmen).

Phase 1: Pilot phase

The pilot phase assessed the feasibility of delivery of questionnaires via our HAPPY London web-based platform. I also monitored recruitment rates, agreement of web-based estimated cardiovascular risk with QRISK2 score, acceptability and compliance of e-coaching, electronic transfer of blood test results into the database, CMR imaging protocol, duration of visits at baseline, 3- and 6-month clinic visits. The pilot phase was planned as a gradual recruitment process. The main idea was to ensure that any technical issues (particularly with the website

functioning, online scheduling, online min-check process and blood result transfer) worked effectively. Recruitment at this stag was limited to the emailed invitation to university staff. The pilot phase lasted about 2 months and only minor modifications were required such as website typo's and availability of questionnaires to the participants (with alerts) at the appropriate visits. An alternative path of finding the questionnaires was developed in case the default method did not work.

Phase 2: Implementation phase

In the main implementation phase we planned to accelerate the recruitment once we were happy that the HAPPY London website, booking system and visit arrangements were running smoothly.

Study Population

I recruited participants from the London area through advertisement and invitations predominantly through primary care practices. I worked with the National Institute of Health and Research (NIHR) Primary Care Research Network to contact GP surgeries that were interested in helping with the recruitment process. The GP sent invitation letters and emails to potentially suitable participants following practice data base searches.

Inclusion criteria

Participants were deemed eligible for inclusion in this study if all of the following criteria were met:

1. Informed consent given by participant (see Appendix for copy of consent form)
2. Between 40 and 74 years of age
3. Had unrestricted access to the Internet
4. Were sufficiently fluent in English language (as judged by the research team). The subject had to be able to understand and comply with protocol requirements, instructions and protocol-stated restrictions

5. An estimated intermediate to high risk for CVD events based on the web-based pre-screening tool "mini-check" (www.happylondon.info), which is based on the non-laboratory FRS (≥10% 10-year CVD risk)
6. Following screening visit participants had to have a 10-year QRISK2 score of ≥10%.

Exclusion criteria

A subject was not eligible for inclusion in this study if they met any of the following criteria:

1. History of myocardial infarction
2. History of stroke or transient ischaemic attack
3. Cardiac sounding chest pain requiring further investigations
4. Current life threatening conditions other than vascular disease (e.g. very severe chronic airways disease, human immunodeficiency virus positive, life-threatening arrhythmias) that may prevent a subject from completing the study
5. Only for subgroup undergoing cardiac contrast-enhanced magnetic resonance studies: Any contraindication to a contrast-enhanced magnetic resonance study, such as known allergies to gadolinium-based contrast agents, severe claustrophobia, pacemakers, defibrillators.

Recruitment

I estimated that I would have to invite approximately 1500 London inhabitants (Figure 3). Our aim was to have a good representation of our South Asian population, ideally about 25% if possible due to the large representation of South Asians living close to our research centre. I utilised various resources for advertisement and invitation ranging from engagement with local community groups, GPs, posters inside London buses and through the primary care research network group and their primary care practice contacts. Posters for the study were displayed in the university and local hospital sites. Invitations were sent through

university and local hospital staff portals. I advertised in local primary care newsletters and at primary care study days to make GPs aware of the study.

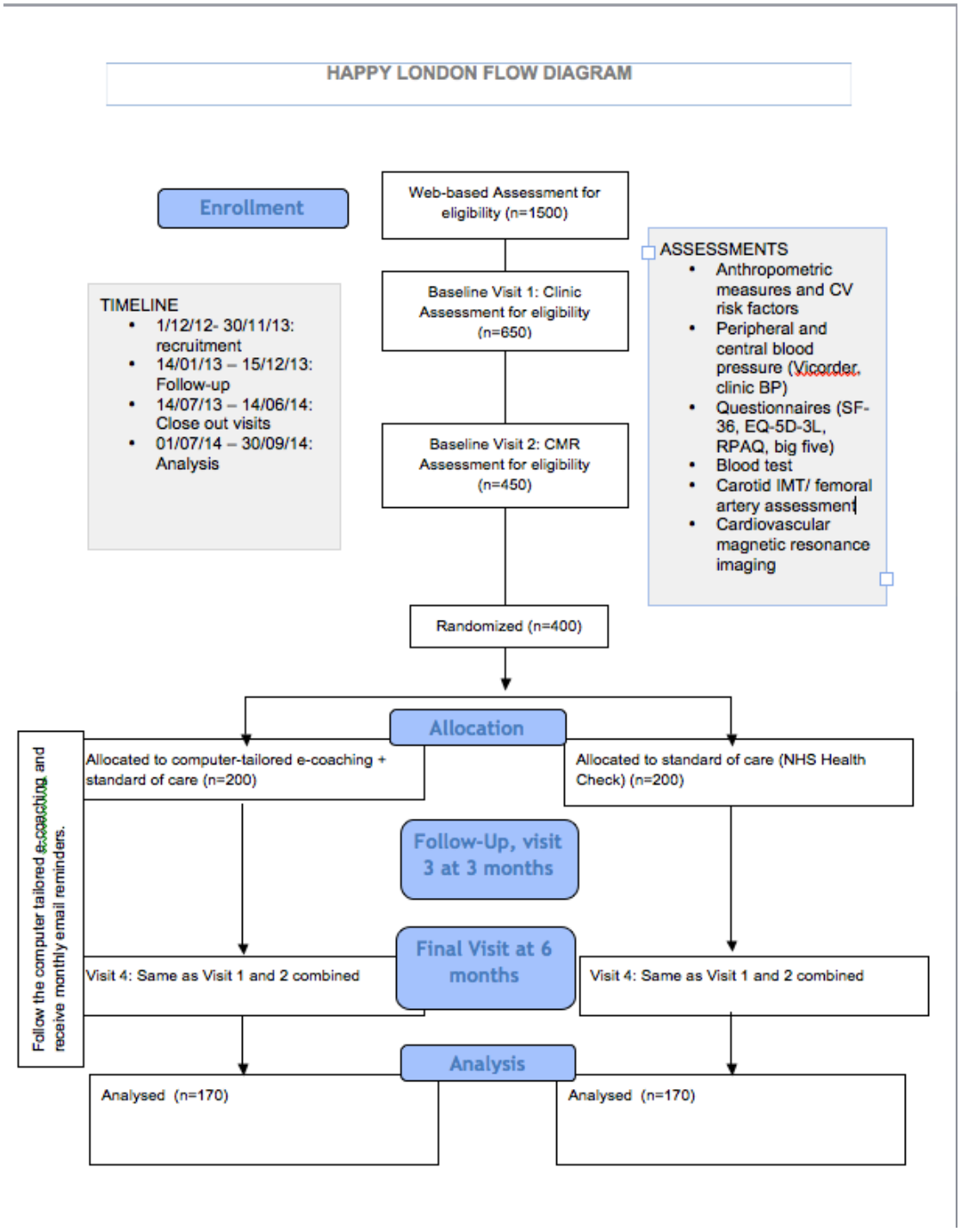


Figure 3. Outline of proposed study

Assessment and Follow up

'Mini-check' - Prior to first visit

Potential participants expressing an interest in this study were directed to the www.happylondon.info website for further information and registration. The CVD risk profile was estimated using a web-based tool ("mini-check"). The purpose of this step was to reduce screening visits. Thus reducing potential cost and other resources required for the study, such as staff and research centre time. In the process I filtered out those who were not eligible due to having too low a risk or not meeting other eligibility criteria. It also allowed us to invite only those that had Internet access.

The mini-check consisted of questions regarding potential exclusion criteria (previous diagnosis of myocardial infarction, stroke or angina). They also had to tick "yes" to a question asking if they had easy access to the Internet. The non-laboratory FRS was calculated based on self-reported age, gender, history of diabetes, hypertension treatment, participant's estimated height and weight and a family history of premature CVD.

If the non-laboratory Framingham 10-year risk scores estimate was greater than or equal to 10% and there were no exclusion criteria, the participant was offered the opportunity to book an appointment for a physical examination using the online booking calendar. If the participants did not want to proceed with the study, a message advised them to discuss the result with their GP, if they were not previously aware that they may have potentially increased risk of developing CVD in the next 10 years. This was in line with the NHS Health check recommendations. Those who had a score of less than 10% were informed that they were not eligible to enter the study.

From this pre-screened population I invited participants with an estimated intermediate to high risk (estimated mini-check 10-year risk score of 10% or more for CVD events), to attend the research centre to assess the actual CVD risk. They were sent an email confirming their chosen appointment slot along with the patient information sheet (PIS) and the consent form that they would sign during

their chosen visit appointment (both forms in the Appendix section). Participants who were potentially eligible for the CMR scan also received a CMR safety questionnaire to review.

Visit 1 (Screening)

The screening visit took place at the Heart Centre, William Harvey Research Institute, Queen Mary University London and lasted approximately 35 minutes. As the visit required the participant to fast for the blood test, visits were limited to the morning time usually starting at 9am and the last slot at 12pm. If participants specifically requested an earlier or later time this was accommodated where possible. Participants who were on treatment were advised to call prior to the visit to get advice on which medications to avoid on the morning visit to avoid potential hypoglycaemia. The research doctor or nurse ensured that the participant was satisfied with the information provided on the PIS and the consent form was completed by the participant and countersigned by a member of the research team who had completed appropriate Good Clinical Practice training. Additional clinical risk profiling was performed based on medical history questions required to calculate the QRISK2 score (diagnosis of atrial fibrillation or rheumatoid arthritis, treatment for hypertension and post code), self-reported smoking status, age, gender and family history of premature coronary artery disease. Anthropometric measurements (height, weight, waist circumference and hip circumference) and BP were taken (See Table 2 for schedule of assessments for each visit). Participants were advised to fast for 8 hours prior to the visit for a fasting blood test checking total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose, hsCRP and renal function (creatinine and estimated glomerular filtration rate eGFR). Based on these measures, the ten-year risk of developing CVD was calculated using the QRISK2 algorithm which is available on their www.qrisk.org website. Participants were categorised as low (QRISK2 <10%), intermediate (QRISK2 10-20%), or high (QRISK2 > 20%). Those in the intermediate or high-risk group were randomised for enrolment into the study with 1:1 allocation to treatment arm.

Table 2. Schedule of Assessment for each visit

Assessments	Baseline Visit 1 (2 to 14 days before)	Baseline Visit 2 (Time 0)	Visit 3 (3 months)	Visit 4 (6 months)
Consent	X	-	-	-
Check for CMR scan contraindications	X	X (For CMR sub-group)	-	X (For CMR sub-group)
Anthropometric Measures	X	-	X	X
CVD risk factors	X	-	X	X
Peripheral +/- central blood pressure (Vicorder)	X (Peripheral only)	X	X	X
Questionnaires (SF-36, EQ-5D-3L, RPAQ)	-	X	X	X
(Big five)		X		
Blood test	X	-	X	X
Carotid IMT and femoral artery scan	-	X	-	X
CMR scan	-	X	-	X
Spirometry			X	

Abbreviations: CMR = cardiovascular magnetic resonance, CVD = cardiovascular disease, IMT = intima media thickness, RPAQ = recent physical activity Questionnaire

The CMR safety questionnaire was also completed (only for the CMR sub-group). If there was no contraindication to CMR and the participant was willing to have one, then the first 50 from the e-coaching group and first 50 from the SOC group were allocated to the CMR cohort. We had to limit the number undergoing CMR due to limited funding. We would ideally have liked to perform more CMR scans to be sufficiently powered to assess change in LV mass over the study period but this was not possible due to limited resources. The decision for eligibility for a CMR occurred prior to randomisation.

Visit 2 (Baseline)

All randomised participants received email confirmation of the second visit appointment with instruction of the procedure to be carried out. They were

advised to avoid caffeine, alcohol and cigarette smoking prior to the visit for a more accurate PWV measurement. This visit could take place in the morning or the afternoon, as it did not require a formal fast. All other visits were preferentially booked in the mornings to make fasting more bearable. Due to the limited staffing resources differing patient preferences I did not attempt to book patients in for the same appointment time for all their visits.

Prior to the second visit all participants were asked to complete a detailed lifestyle questionnaire that would form the basis for lifestyle advice in conjunction with discussion of the results from the screening visit (e.g. BP, blood tests, BMI). The questionnaire assessed recent dietary habits during a typical week, including fruit, vegetable, dairy, meat products including processed meats, daily alcohol intake over the preceding week, questions to gauge psychological, stress and anxiety levels and physical activity questions that tried to elicit duration of moderate, vigorous activities of more than or equal to 10 minute blocks.

During this visit participants were informed of the results of the risk assessment (conforming to information that would normally be available in a primary care setting) and received personalised advice from the research doctor in accordance with guideline recommendations from the NICE and the ESC regarding smoking cessation, weight loss, BP control etc. The personalised lifestyle and risk factor advice was given over 10-15 minutes, based on information from the lifestyle questionnaire and the information available from the first visit including blood test. Additionally Vicorder assessment and ultrasound scan (for carotid plaque, CIMT and femoral artery assessment (30 minutes) were performed.

Participants randomised to the e-coaching group were shown how to use the personalised website (10 minutes). Participants were asked to complete additional questionnaires (SF-36, EQ-5D-3L, RPAQ and Big 5 personality trait (developed with Professor Thomas Dohmen who is a health economist), 30-40 minutes) on the day of the visit or at least within 2 weeks of the visit date.

If appropriate, participants were referred to their GP for further tests or interventions (such as initiating BP medication or referral for specialist opinion). I

also determined the quality of life (SF-36 and EQ-5D-3L) as well as self-reported physical activity (RPAQ) based on validated questionnaires.

Those undergoing a CMR scan (96 who were actually scanned) had insertion of a venflon for standard CMR gadolinium based contrast agent to be administered during the scan. The contrast agent has very low risk of side effects and I did not include anyone with significant renal impartment (eGFR<30 mls/min/1.73m^2) to avoid risk of nephrogenic systemic sclerosis. Standard contra-indications applied to CMR imaging and I routinely checked for these (e.g. pacemaker, defibrillator, vascular clips, cochlear implants, significant claustrophobia). The CMR scan took about 60 minutes.

Participants were informed that there was very little risk with taking part in the study. Some of the potential risks with contrast agent injection (rare) were explained in the patient information sheet. They were also told prior to the investigations that they would only receive information that they would expect to get from their GP (such as the blood test results and blood pressure readings). Findings from other scan and test results (PWV, ultrasound and CMR) would not be conveyed to the participant unless there was a serious unexpected finding that required urgent attention. Part of the reason for withholding this information was to avoid test results potentially influencing behaviour change and thus making it difficult to answer the study questions. The PIS also mentioned that we would inform the GP about important findings during the study with their permission (this was obtained on the consent form). At the end of the study they were shown the images of their carotid ultrasound and if there was atheroma present. For those who had a CMR scan they were shown mainly the cine/ movie images of their heart and a brief description of the overall visual function.

Visit 3 (3-month follow-up)

The 3-month follow-up visit involved repeating most of the assessments from the baseline visit 1 (35 minutes), including blood test, BP measurements, anthropometric measurements (weight, waist and hip circumference), lifestyle questionnaire, SF-36, EQ-5D-3L, RPAQ and non-invasive measures of vascular

function using the Vicorder® device. Additionally, spirometry was performed once during the study and mostly during this visit.

Visit 4 (6-month follow-up)

The 6-month follow-up visit involved repeating all assessments from visit 1 and 2 for all participants (50 - 60 minutes), including blood test, BP measurements, anthropometric measurements (weight, waist and hip circumference), SF-36, EQ-5D-3L, RPAQ and non-invasive measures of vascular function using the Vicorder device. The CIMT and femoral artery assessment were repeated. In addition, the subgroup that underwent a CMR scan at baseline had the same CMR protocol repeated at the 6-month follow up visit.

Informed written consent

Participants were asked to complete the consent form once they were satisfied with the aims, methods, anticipated benefits and potential hazards of the study. This information was provided prior to the visit in the form of the PIS. At the visit the researcher also provided a brief summary and clarified any queries or concerns from the participant. The Investigator, or appropriate Good Clinical Practice trained person delegated by the Chief Investigator, obtain written informed consent from each subject prior to any participation/study specific procedures.

Proposed sample size

I based our sample size calculations on using a two-sample t-test with equal variances. The Type I error was set at 5% (two-sided). The inputted standard deviations were based on published inter-study reproducibility data for our primary end point of PWV: Vicorder measured PWV 0.29 m/s [172]. Aerobic exercise in pre- and stage-1 hypertensive patients for example reduced central PWV after 4 weeks by 1 m/s (12.1 +/- 0.8 m/s to 11.1 +/- 0.8 m/s) [173]. The effect size is likely to be less than what is frequently seen in antihypertensive medication trials after

10-12 months. Sample sizes required for type II errors of 5, 10 and 20% and for four different effect sizes are presented in **Table 3**.

In summary, we proposed a sample size of 200 patients in each treatment arm assuming a dropout rate of 15-20% at the follow-up visit and having enough power (80%) to detect a small but clinically relevant change in PWV. I also include a sensitivity table for sample size calculation for assessing change in LV mass change using CMR. Although I was not sufficiently powered to detect change in LV mass with only 50 people in each treatment group in the CMR sub-study, I wanted to assess for effect size of CMR surrogate markers with lifestyle changes over a short period of time (6 months). This would be useful for design of future larger phase 2 primary prevention trials with behavioural interventions.

Table 3. Sample size calculations with sensitivity analysis for LV mass and PWV

PWV

Type 1 error 5%	95% power	90% power	80% power
0.1 m/s	220	178	133
0.15 m/s	99	80	60
0.2 m/s	56	46	34
0.25 m/s	36	30	23

LV mass

Type 1 error 5%	95% power	90% power	80% power
2g/m²	182	147	110
3g/m²	82	66	50
4g/m²	47	38	29
5g/m²	30	25	19

Type I error, 5% (two-sided), two-sample t-test with equal variances, standard deviations of difference for LV mass index 5.27 g/m2 and 0.29 m/s for pulse wave velocity. [172,174]

Randomisation

Randomisation was based on random numbers created in excel 2011 for Mac with 1:1 allocation. 2 sets of four hundred randomised numbers were generated to allow stratification (2 strata). One set was for moderate risk (QRISK2 10-20%) and the other was for high risk (QRISK2 ≥ 20%). Numbers ending with an even digit

were allocated to e-coaching; numbers ending with an odd digit were allocated to the SOC treatment arm. The sequence was concealed to researchers involved with recruiting and assessing participants. Randomisation into the treatment or control group was performed after confirming eligibility. The randomisation tool was created using PC software and the sequence was incorporated into an in-house computer programme, which allocated the treatment group once participant identifier, and their QRISK2 score was entered, to enable stratification. Our department physicist who was independent of the recruitment or randomisation of the participants developed the computer programme.

Website hosting

The website was hosted in the Netherlands through the HAPPY Globally Foundation. The web team ensured that Dutch and UK legal standards were met to enable secure information transfer. The website team dealt with technical issues arising during the running of the HAPPY London website.

Concurrent medication or treatment

Patients were advised to continue regular medications. The research team initiated no medications. However, in cases where medication was deemed appropriate based on guideline recommendations for cholesterol or BP, a letter of recommendation was sent to their GP. Management was at the discretion of the GP and according to GP's local protocols.

Assessment of safety

The study was subject to monitoring by the Sponsor, Queen Mary University of London, in accordance with their policies in conjunction with the standard quality management policy of the William Harvey Heart Centre. Any monitoring findings should have been relayed to the Chief Investigator and acted in the best interest of participants, sponsor and funder.

Subject withdrawal

Previous and current studies under the umbrella of the Happy Globally Foundation suggested that subjects are willing to participate in this kind of study[83]. Based on previous experience I estimated a dropout of up to 15% at the 6-month follow-up visit. Compliance to the e-coaching tools was measured as frequency of HAPPY London Web site log ins.

In case of subject withdrawal, I aimed to understand their reasons, although the patient was not obliged to give the reasons for withdrawing consent. Withdrawal reasons were critically appraised but did not require protocol amendment request to the ethics committee.

In the trial I used the intention to treat approach and included all the available data for analysis, unless a patient withdrew consent to use the data. In such case that particular patient's "intention" to participate in the trial was reported as n=1 number of patients included in the trial.

Assessments

Blood Pressure

BP was taken at screening, 3 months and 6 months. The cuff was deemed an appropriate size for the individual if it covered at least 2/3 of the arm. Systolic and diastolic BP (BP, in mmHg) were measured with a cuff around the left arm after relaxing in a seated position for at least 5 minutes with the left arm rested on table at about the level of the nipple. Legs were uncrossed and the participant was requested not to talk, in accordance with NICE guidelines [28]. At least 2 measures were taken using a fully automated BP monitor (Calibrated Omron 705IT BP). This was repeated if there was a difference of 10mmHg in the systolic or 5mmHg in the diastolic between the two measures. An average of 2 consistent measures was recorded. We did consider including 24 hour blood pressure monitoring but due to limited finances and staffing resources, were unable to include this in the study.

Anthropometric measures

Height (in cm) was measures on bare feet with a portable device (Seca 704s, Hamburg, Germany), which also had a calibrated scale for the body weight (in kg) with the participant in light clothing and without shoes. Height was only measured at the first visit and along with the serial weight measures. BMI was calculated using the formula - BMI= weight (in kg)/ height^2 (in meters).

Waist circumference (in cm) was taken with a measuring tape at the mid point between the lower border of the ribs and the upper margin of the pelvis. Hip circumference was measured at the widest observed point of the hip.

Biochemistry

Venesection was performed at the first visit with a single serum tube of 4-5 mls taken following at least 8 hours of fasting. The serum sample was centrifuged for 30 minutes after the sample was taken and then sent to the lab for analysis.

Blood tubes were labelled with the subjects' number and date of collection. Samples were analysed in The Doctors Laboratory, 60 Whitfield Street London W1T 4EU. I asked participants to allow long-term storage of samples for future analysis of biomarkers (see consent form in Appendix).

The parameters measured were total cholesterol (mmol/l), HDL (mmol/l), LDL (mmol/l), triglycerides (mmol/l), hsCRP (mg/l), glucose (mmol/l), creatinine (umol/l) and eGFR (mL/min/1.73sqm). The blood tests were performed 3 times in total, with a minimum of 8 hours fast, at the screening visit, 3 months and 6 months.

Screening visit questionnaire

At the screening visit participants were asked about all the variables in the QRISK2 scoring system, namely, gender, ethnicity, home address postal code for the Townsend deprivation score, first degree family history of premature coronary

artery disease (AMI or angina <60 years of age), antihypertensive medication prescription, history of diabetes, atrial fibrillation or rheumatoid arthritis.

QRISK2 risk score estimation

The 10 year QRISK2 score was computed using the website www.qrisk.org once blood tests result was available for the screening, 3-month and 6-month visits. This usually occurred on the next working day after the visit. However, during the course of the study its developers updated the QRISK2 algorithm. To ensure I used the most up to date validated QRISK2 algorithm we recalculated scores for all visits at the end of the study. The updated QRISK algorithm scores were used for the final analysis.

Questionnaires

Serial standardised questionnaires were administered to assess change in quality of life (SF-36 and EQ-5D-3L surveys) and physical activity (RPAQ). These questionnaires were chosen following advice from Professor Myriam Hunink, a Professor of Epidemiology and Radiology at the Erasmus Medical School and a visiting Professor at the Harvard School of Public Health. They have been validated and used in the assessment of quality of life change.

Additional questions, designed by the web team, to assess lifestyle factors were administered. The above questionnaires were completed at baseline, 3-months and 6-month visits. A Thomas Dohmen questionnaire to determine the 'big five' personality traits was also completed once around the time of visit 2. For the purpose of the thesis only the results from the lifestyle questionnaire (developed by the web team) will be provided. The results of the validated RPAQ, SF-36 and EQ-5D-3L will not be presented in this thesis nor the result of the Thomas Dohmen questionnaire. These data will be analysed at a later date to determine the impact of the study on quality of life and to aid economic and compliance evaluation.

Vicorder measurement of pulse wave analysis and pulse wave velocity

Arterial stiffness was determined non-invasively by (i) PWA and (ii) PWV (Vicorder). Performing PWA and PWV measurements took about 15 minutes.

Pulse wave analysis

The research nurse or I performed the PWA and CFPWV measurements. The patient was allowed to lie on the bed for about 10-15 minutes before the measurements were taken. The room was temperature controlled and the patient was in a supine position. Patients were specifically advised to refrain from caffeine, alcohol and smoking for at least 8 hours prior to the assessment. The Vicorder measurements were obtained at the baseline visit, 3-months and 6-months follow up visits. PWA was measures first followed by the CFPWV.

A brachial BP reading was taken just prior to Vicorder measurements using the same automated OMRON machine used for other BP measurements in the study. This BP was used to calibrate the peripheral waveforms obtained from the Vicorder. The Vicorder digitally computed a brachial pressure wave trace with the cuff statically inflated to 70 mmHg using a high-fidelity cuff and volume displacement technique on the left arm in all cases. A brachial-to-aortic transfer function was then applied by the Vicorder software to calculate the waveform and values for central BP [102]. The first and second central systolic peaks were automatically identified by the software and used to calculate the AI (difference in amplitude between first and second systolic peak/pulse pressure x 100). The measurement was repeated 3 times and average of 3 good quality traces was recorded. At least 10 consistent (ie. no ectopic beats or artefact) beats were required for each PWA measurement.

Pulse wave velocity

Change in CFPWV derived from the Vicorder device was the primary end point. I used this surrogate marker, as it appears to have one of the best profiles from the possible surrogate markers available compared to other biomarkers that could be

used as potential surrogate markers for CVD (Table 4). For the purpose of this thesis only the results of the oscillometric PWV (i.e. the CFPWV derived from the Vicorder). The results of the CMR derived PWV, including correlations with the Vicorder derived CFPWV, will be presented in future publications as it does not constitute the primary end point and need further analysis before being published.

Table 4. Potential surrogate markers against working group criteria of a vascular biomarker. Adapted from ESC Working Group criteria [87]

	Carotid ultrasound	CFPWV	Central haemodynamics/ wave reflections	HsCRP
Proof of concept	4+	4+	4+	3+
Prospective validation	3+	4+	3+	3+
Incremental value	3+	4+	3+	2+
Clinical utility	2+	3+	2+	3+
Clinical outcomes	1+/-	1+	1+	2+
Cost-effectiveness	1+	1-	1-	1+
Ease of use	2+	3+	3+	4+
Methodological consensus	2+	3+	3+	3+
Reference values	Yes	Yes	Yes	2 mg/L cut-off

Abbreviations: CFPWV, Carotid-femoral pulse wave velocity; ESC, European Society of Cardiology; hsCRP, High sensitivity C-reactive protein
Grading: Positive number ranging from 1+ to 4+ with a higher number suggesting better evidence. 1- suggests that evidence is lacking

For the assessment of CFPWV, cuffs were inflated gently around the thigh and neck, to detect the timing of the waveform between these sites, from which the velocity was calculated. A 10cm wide BP cuff was placed around the upper left thigh to assess the femoral pulse and a 3cm partial cuff was placed around the neck at the level of the left carotid artery. The aortic path length was estimated from the body surface markings according to the instructions from the manufacturers (for the Vicorder device), from the tip of the suprasternal notch to a defined point on the upper part of the femoral cuff (first white stitch mark closest to the groin). The cuffs were simultaneously inflated to 65 mmHg and 2 waveforms of high quality were recorded simultaneously for a target of about 10 consistent beats using a volume displacement method. The foot-to-foot transit time was measured and values for carotid-femoral PWV were automatically obtained from the computer software (Figure 4).

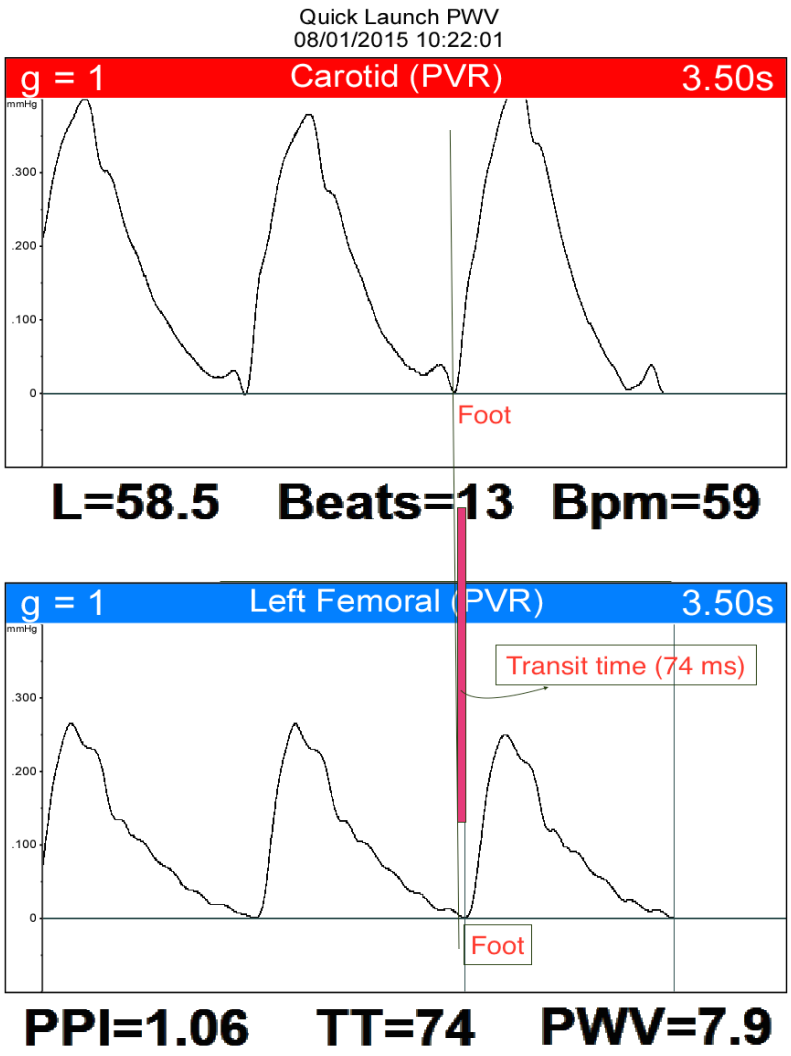


Figure 4. Method for calculating the transit time (TT) used to derive CFPWV, using the 'foot-to-foot' using the Vicorder device.

The average of 2 PWV measures was used. PWV measurements that were suboptimal due to poor quality were excluded if they met 2 criteria; 1. If the 2 measures were > 1m/s different from each other at the same visit suggesting significant variability in measure and thus reduced accuracy. 2. If the semi-automated waveform detection by the computer software appeared grossly inaccurate. Quality check was performed by 2 researchers blinded to the intervention (Armida Balawon and I).

I repeated the PWV in 11 patients for intra-observer reproducibility. I performed the PVW measure as usual then 15 minutes later repeated measurement according to the protocol after the cuff had been removed and the participant allowed to walk around the research department.

Participants were advised to wear thin lower trousers or shorts to facilitate putting on the femoral cuff. If participants had thick trousers or jeans they were requested to remove their trousers and were covered with a bed sheet once the cuff was attached. I had a female researcher (Armida Balawon) who I trained to perform both the femoral cuff attachment (for CFPWV) and femoral artery ultrasound (for presence of femoral artery plaque). Female participants were given the option for a chaperone or a female to perform the tests. Only about 4 females specifically requested a female to perform it for them and the remaining participants accepted the procedure. None participant refused either the femoral cuff or ultrasound.

Carotid intima media thickness

CIMT was determined non-invasively using an ultrasound machine (CardioHealth System, Panasonic). The participant was in a supine position with the head rotated 45° towards the contralateral side of the carotid artery being measured. Automated measure of the CIMT was taken from the posterior artery wall of both carotid arteries with 24 spatial measurements over a 1cm region of interest, 1cm caudal from the flow divider located at the carina of the common carotid artery bifurcation. A vascular probe (Panasonic) was used, with the frequency set at 9 MHz, according to the protocol outlined by the American Society of Echocardiography consensus statement [150]. I assessed for evidence of carotid plaque and measured an automated CIMT. Using the same ultrasound probe, I assessed the femoral arterial bed in the groin to look for evidence of atheroma. The CIMT was automatically calculated once the ultra-sonographer obtained a good quality trace of the posterior wall of the carotid artery. The ultrasound procedure on average took between 5 to 10 minutes.

Cardiovascular magnetic resonance assessment

The 60 min CMR scan was performed at the Barts Health NHS Trust CMR unit. This process began with completing a standard CMR safety and consent form. Questions were designed to identify any internal or external ferromagnetic material or

implants, particularly pacemakers or implantable defibrillators. Questions were also specifically asked about preceding history of blackouts or seizures, any problem with previous medical scanning and any history of renal impairment. All participants had a renal function test 2-4 weeks prior to the scan and if eGFR was noted to be less than 30ml/min/1.73m^2 then the scan was deemed to be contraindicated due to the risk of nephrogenic systemic fibrosis. This safety precaution was to ensure for a second time that the participants did not have any contraindications. The subsequent visits required all the questions to be completed again.

I performed the CMR scans under the supervision of an experienced CMR technician or CMR physicist. CMR scanning required lying still in a supine position attached to an ECG with the participant wearing ear protection. The subjects were asked to breath hold in expiration for up to 15 seconds during each image acquisition throughout the scan time with sufficient time in-between to breath normally. Near the end of the investigation a CMR contrast agent was administered (Dotarem, Guerbet).

Analysis of CMR data was performed blinded to the intervention. The analysis entailed LV volumes and mass determination, measures of global and regional LV systolic and diastolic function using steady state free precession imaging and tagging. Aortic stiffness was assessed using global PWV (results of the CMR derived PWV will not be presented in this thesis and will form part of further work that our research group and I will undertake in the future towards publications in peer reviewed journal) and regional assessments (aortic distensibility of the ascending thoracic, descending thoracic and abdominal aorta). I acquired phase contrast imaging for PWV. One pre and 3 post contrast 'Look Locker' type sequences were acquired for assessment of fibrosis. Late gadolinium enhancement images were obtained following gadolinium-based contrast agent administration to allow assessment of scar and fibrosis in the heart muscle.

CMR imaging was performed on a 1.5T CMR system (Achieva, Philips, Netherlands) using a software release 3.2 and cardiac package installed. A dedicated 32-channel cardiac coil was used. These CMR measurements were performed at baseline and after 6 months using the same scanner model and software.

The aorta was assessed at 3 different levels. Perpendicular to the ascending thoracic aorta (TAA) at the level of the main pulmonary artery, perpendicular to the descending thoracic aorta (TDA) at the level of the main pulmonary artery and the abdominal aorta (ABA) 10cm below the TDA point. At each of the levels SSFP cine images and phase contrast images were obtained.

Oblique sagittal views of the course of the aorta were obtained to allow measurement of path length between the 2-dimentional flow measurement points and were used to plan these sequences. The calculation components for PWV are similar to those described for the Vicorder. The aortic view was used to measure the distance between 2 segments and post-processing analysis would help to obtain the transit time between these 2 points (Figure 4). Thus PWV = distance between 2 points / transit time.

TDA

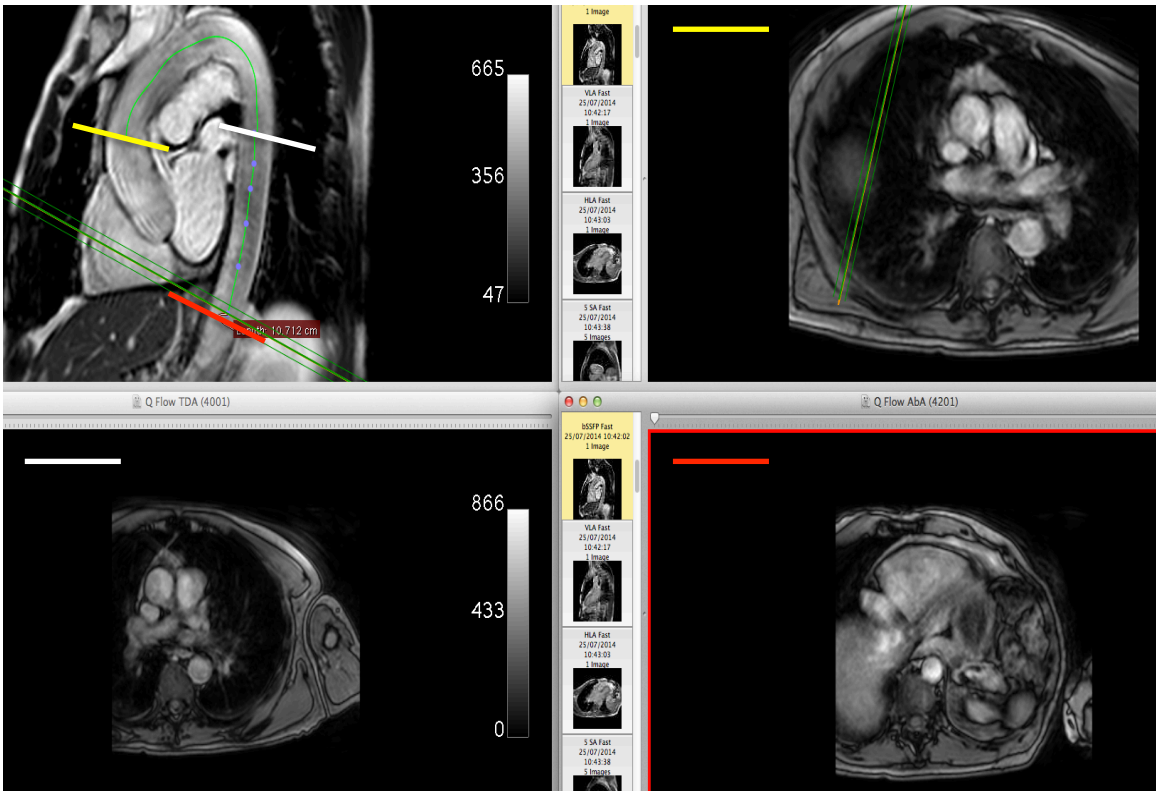


Figure 5. Calculation of aortic path length. Aortic view (top left panel) used to measure distance from TDA to ABA in this image using the reference point of ABA velocity-encoded phase-contrast sequence to identify the ABA position. Distance from TAA to TDA was measured using the TAA and TDA sequences to guide start and end point of line.

The velocity-encoded phase-contrast sequence was set to 200 cm/s and was adjusted in the case of aliasing. Spatial resolution was 1.22mm X 1.22mm. Repetition time was 3.9 ms, flip angle 15 degrees, slice thickness 10mmRetrospective ECG triggering was used with 2 views per segment. The temporal resolution was 22 ms. CMR PVW data will be used for future analysis and not included in this thesis.

Peripheral BP was measured using a CMR compatible oscillometric sphygmomanometer (Vicorder, Skidmore medical, UK) and the central BP was estimated using a validated transfer function used in calculating distensibility where : Distensibility (10^{-3} $mmHg^{-1}$) =
((Maximum Area (cm2) – minimum Area (cm2)/(PP x minimum Area (cm2)) x 100

Minimum and maximum values were obtained using an in-house semi-automated border-tracking programme written in MatLab (version 8.2), which measured the inner lumen of the vessel[175]. The three levels of the aorta (TAA, TDA and ABA) were analysed separately. The programme then tracks the endoluminal border through all phases of the cardiac cycle and measured the cross-sectional area for each phase. This was achieved by the radial detection of a signal change. A manual step of identifying the centre of the vessel was also required. The automated detection was only modified manually if there was more than 1 pixel discrepancy between the investigator visual assessment and the automated contour outline.

Left ventricular volumes and function

Vertical long axis and horizontal long axis images were first acquired following a pilot sequence. These images were used to acquire short axis planning views. True 2 and 4 chamber views were obtained using the short axis planner and horizontal and vertical long axis images. A perpendicular slice though the long axis of the LV using both the 2 and 4 chamber cine images were used to acquire the short axis SSFP cine slices from the atrio-ventricular groove to the cardiac apex. Acquisitions were performed breath held at end-expiration, using retrospective ECG gating. The standard sequence settings for our research scans were: echo time 1.44 ms,

repetition time 2.9 ms, in-plane field of view 205x380 mm, acquired voxel size 1.9×2.04 mm (reconstructed to 1.46×1.48 mm), acquisition matrix 108×186 (frequency encoding × phase encoding), slice thickness 8 mm and a 2 mm gap between slices, 30 reconstructed frames per cardiac cycle (typical temporal resolution of 46 ms for a heart rate of 60 beats per minute), and a 60° flip angle.

Post processing of biventricular endocardial contours was performed manually using the short axis cine stacks. End-diastolic and end-systolic frames were identified and contoured. The papillary muscles were excluded from the myocardial mass but included in the blood pool. These were summed for the whole ventricle using the CVI42 semi-automated software (Circle Cardiovascular imaging Inc., Calgary, Canada). As per recommendations basal slices were only included for LV analysis if more than 50% of the lumen was surrounded by myocardium [176].

Epicardial contours were only manually segmented at end-diastole for the LV. The method of disks or Simpson's rule was applied to calculate the ejection fraction. LV mass was derived from the myocardial volumes multiplied by the density of the myocardium (1.05g/ml). Parameters derived for the chamber volumes were indexed to body surface area (BSA) as determined by the Mosteller formula.

Spirometry

Spirometry was performed within in one year of visit 2 using equipment that met the minimum performance recommendations of the American Thoracic Society / European Respiratory Society task force (Microlab3500, Micromedical, UK) [177]. At least 3 valid spirometry efforts were attempted (but no more than 8). Spirometry was added following a protocol amendment in March 2014. The addition was to allow further assessment of cardiovascular risk and its association with lung function for future analysis.

Results of scan and incidental findings

Participants were not informed of the results of the MRI, carotid ultrasound or the Vicorder measurements during the study. They were, however, informed about the findings in detail at the final visit. This was decided on the basis that they were

tests that would not ordinarily be performed by their primary care team and to avoid causing any confounding to the results of the intervention under study. Additional test information that potentially leads to lifestyle modifications would have biased the results.

Participants were, however, informed if any serious findings became apparent on the tests and the findings were also communicated to the GP, with the patients' permission. Discussion about serious findings took place at the time of the investigation or once a specialist opinion was obtained e.g. from a radiologist (suspicious lung lesions) or cardiologist (for suspicion of previous infarction).

Where evidence of a carotid stenosis of >50% was identified the participant would be referred via the GP for a vascular surgical opinion. This was based on local protocol and advice from the vascular team in our institution. If they were not already on a statin then this was recommended by letter for the patient to take to their GP, in addition to antihypertensive medication if the BP was elevated.

Incidental myocardial infarction detection with CMR scanning in asymptomatic older adults is recognised. A study suggested that the incidence in adults (ages 67–93 years) may be as high as 17% [178]. I thus expected to find such incidental findings especially since our cohort had an elevated cardiovascular risk. If an infarction was detected this was confirmed with the study principal investigator (Steffen Petersen, a cardiology consultant specialising in CMR). The patient was informed and the result communicated to the GP. If the participant was not already on medication recommended for secondary prevention, then this was also recommended for initiation.

In case of suspicion of other significant cardiac or extra-cardiac finding this was communicated to the participant after consultation with a radiologist and suggested further investigations were carried out at our institution or via the GP depending on the urgency, patient preference and convenience.

Intervention

E-coaching

Computer-tailored e-coaching was provided to the intervention group for 6 months ("HAPPY London") in addition to the SOC that would be expected from NHS primary care visit. HAPPY London consisted of frequent personalised emails to update the individual profile with behaviour questionnaires on the identified sub-optimal behaviours. The tailoring was based on a combination of feedback to the participant's motivation for change, feedback comparing participant's behaviour to current recommendations, feedback comparing participant's previously set goals to the participant's behaviour, the behaviour of peers to the participant's previous behaviour, feedback tailored to participants' self-efficacy, their intentions and attitudes and the potential benefits or barriers to behaviour change. The website contained educational tools, information on support websites such as NHS Choices, links to social media and other health websites and health news items. See chapter 4 for more details on the website development and functions.

For those in the active intervention or e-coaching arm, in addition to the face-to-face advice, they also received personalised web-based advice according to results of the lifestyle questionnaire with a computed lifestyle score out of 10, with 10 being excellent) and a heart risk score. Due to technical and potential copyright issues with the QRISK2, I opted to use the FRS for the purpose of the web-based information. If there was a significant discrepancy between this and the estimated QRISK2 score as computed I explained this to the participant.

The e-coaching group received an additional 10 minutes (on top of the 10 - 15 minutes discussing results and suggested lifestyle interventions that both groups received). This was to show them how to navigate through the website and personalise some of the features of the web tool and emails. Ideal targets were highlighted as goals and the information (lifestyle factors, lifestyle score, risk factors and risk score) was updated at 3 and 6 months allowing the participant to view their progress, to provide dynamic tailoring which has been shown to

increase efficacy over time [6]. Participants were not given the option to interact with the system. They could not ask questions or make comments about specific aspects of their personalised information in order to limit health care resources and test the self-efficacy of the website. Aspects of behavioural change that were addressed included goal setting, social support, review of behaviour goals and the use of prompts.

E-coaching involved computer-tailoring, a method of assessing individuals' suboptimal lifestyle and risk factors and selecting communication content using data-driven decision rules that produce feedback automatically from a database of content options. Participants had personal login and passwords. Information was provided as written information on the website. Lifestyle score, as a number and in graph form was provided for each visit to allow participants to view their progress. This included colour coding for easy summary. Lifestyle score of over 8 out of 10 had a green bar, between 6-8 out of 10 an orange bar and less than 6 a red bar. Lifestyle and CVD risk factors were also colour coded for each participant with coloured heart shapes. Green smiley hearts represented optimum factors, orange heart shapes represented factors that were mild to moderately suboptimal and sad red heart shapes represented more than moderately suboptimal factors that required more attention. Participants were advised to log in as often as they wanted. I did not specify a minimum or maximum number of times they were required to log in. I measured the engagement with the platform based on the number of times the participant logged into their account.

Control group - Standard of care

This involved face-to-face advice based on the results of the BP, blood test results and lifestyle questionnaire. Factors deemed to be suboptimal were discussed and advice given mainly based on advice that would be obtained during an NHS health check visit (10-15 minutes) and based on contemporary guidelines [17,153]. If pharmacotherapy was felt to be required, this was communicated to the primary care clinician to prescribe according to local policy.

For those in the control arm or SOC group they did not have access to their information online but information on the result of measurements from the screening visit and personalised advice, based on the lifestyle questionnaire, was the same as that given to the e-coaching group.

Visit 2 - Lifestyle advice for all participants

Participants in both the e-coaching and SOC group received lifestyle advice tailored to their risk factors and sub-optimal lifestyle factors. This was based mainly on 2012 guideline recommendation from the ESC and subsequently included the updated advice guideline recommendations from the Joint British Society consortium version 3 (JBS3), which was published during the study period (April 2014) [17,153]. All participants were informed about their BP and whether this was optimal or not. A BP of >140/90 mmHg was classified as high. Below is a brief outline of the advice given to participants based on individually identified suboptimal factors.

Fruit and vegetable

It was advised that at least 5 portions of fruit and vegetables be consumed daily in accord with national guidelines. It was also discussed that based on epidemiological data vegetables appear to have more benefit then fruit and thus a ratio of about 3 vegetables to 2 fruit was suggested.

Alcohol

Those who drank alcohol were reminded that the national government guidelines for men was to consume <21 units of alcohol for men and <14 units for women. However, it was also mentioned that studies suggesting the potential benefits of alcohol (namely with wine) suggested consuming moderate alcohol as <14 units for men and <7 units for women, spaced evenly over the week.

Physical activity

As per recommendations from the national guidelines participants were advised to do at least 30 minutes of moderate physical activity most days of the week (at least 5 days) amounting to ≥ 150 minutes per week. This was recommended in a minimum of 10-minute blocks.

It was advised that activities such as brisk walking and certain household chores could count as moderate, whereas vigorous activity such as running possibly counted for twice the moderate amount.

Smoking

For current smokers the benefits and harms of smoking were emphasised. In particular, participants were advised to choose a date for quitting smoking and to stick to this. They were also reminded that in addition to over the counter and self-help tools their primary care physician could also assist with referral to a smoking cessation counselling service or nicotine replacement therapy.

Age and family history

Participants were informed that older age is a risk factor for CVD and although this is not modifiable maintaining a healthy lifestyle and maintaining other modifiable risk factors under control may partly compensate for the effects of aging.

Likewise, for a family history of premature CVD may confer higher risk and this should be borne in mind and be a motivational factor with regards to improving other lifestyle factors.

Blood pressure

Lifestyle advice for those with elevated BP whether on antihypertensive treatment or not was based around advice from NICE and the British Hypertension Society,

namely being physically active, weight loss if overweight or obese, reducing alcohol intake if more than moderate and reducing salt consumption [28].

If the BP was >180/100 mmHg then it was recommended that they visit their GP urgently to have their BP rechecked with a view to initiating antihypertensive treatment with a letter for the participant to take to their GP. If the BP was lower but there was evidence of renal impairment or diabetes then they were still recommended to see their GP.

Cholesterol lowering

Participants were informed about the result of their cholesterol with the target of total cholesterol of <5 mmol/l corresponding to LDL cholesterol < 3 mmol/l as the minimum requirement, with the suggestion that more recent guidelines suggesting even lower cholesterol targets.

To lower the cholesterol levels lifestyle factors were discussed namely avoidance of processed food and foods containing those with trans-saturated fats. It was recommended that red meat consumption be moderated to about 1-2 times a week and to reduce junk food intake such as cakes, pastries, biscuits and crisps. Fish consumption was encouraged 2-3 times a week with 1 portion of oily fish per week.

Physical activity, weight reduction, increased fibre, fruit, vegetable, polyunsaturated oils such as olive oil, nut consumption (walnuts, brazil nuts, almonds etc.) up to a handful per day and oats were suggested as a way of improving cholesterol levels.

Weight reduction

Recommendations for those who were overweight (BMI ≥25 kg/m2) were made to try and combine dietary changes with increased physical activity. The Mediterranean type of diet, as an example, was recommended with emphasis on reducing portion sizes, and avoiding/ moderating foods high in sugar and fat.

High-risk group

Those participants who had an elevated QRISK2 of ≥20%, a history of diabetes or if the cholesterol level was significantly elevated, were recommended to consider statin therapy as primary prevention medication as per NICE guidelines at the time of the study[179]. Participants with a lower QRISK2 score between 10 and 20% were also recommended a statin in addition to lifestyle modification if the cholesterol was significantly elevated or they had a combination of other risk factors, such as diabetes. For those who opted for lifestyle intervention alone in the first instance a review period of 3 to six months was agreed to reconsider management dependent of changes in risk score and biomarkers.

Ethics

All aspects of the study were conducted in accordance with the principles of the Declaration of Helsinki. The HAPPY London study received a favourable ethical opinion from the National Research and Ethics Committee London – Central on February 21, 2013 (13LO/0094). The ethical approval letter can be found in the Appendix section. Prior to receiving the final ethical approval and following the meeting I attended with the Research and Ethics Committee the 8 main points they wanted addressed or clarified are included below as found in the provisional ethics approval letter.

Further information or clarification required:

1. Add Yes/No boxes to consent form to participants to say they do not give permission for long-term storage use of blood samples.
2. Offer an opt-in for with regard to notifying participants GP's of any important results.
3. Add a statement to the patient information sheet that data protection is in place.

Amendments to the patient information sheet.:

4. Modify the first sentence of the patient information sheet ' we want to help prevent you from having a heart attack or a stroke'. This seems that it is designed to scare participants.
5. Amend point 3 of page 2 of the patient information sheet to advise participants on their risk profile.
6. Explain in lay terms in the patient sheet ' gadolinium based contrast agent'.
7. Remove the following wording from the last paragraph of on page 4 'but would make your participation even more valuable'.
8. Add to point 7 of the patient information sheet further detail of what the computer programme offers and what the participants are expected to do.

Funding sources

The work was primarily funded as part of a Barts Charity large project grant (437/1412). This work also forms part of the research areas contributing to the translational research portfolio of the Cardiovascular Biomedical Research Unit at Barts, which is supported and funded by the NIHR. The HAPPY London team acknowledges the support of the NIHR, through the Clinical Research Network. The Barts Charity and the NIHR had no role in the design of the study; the collection, analysis, interpretation of the data; or the decision to approve publication of the finished manuscript.

Statistical analysis

Analysis was done on an intention-to-treat basis, but secondary analysis compared treatment effects as per protocol (as treated). Mean ± standard deviation was recorded for normal distribution. Median and interquartile ranges were used for data that were not normally distributed.

My null hypothesis for the primary endpoint of PWV was that there would be no difference in the change of PWV between the two treatment groups. T-test was used for normally distributed continuous measures and Chi2 for categorical variables. Where variables were not normally distributed, non-parametric tests were utilised (Mann-Whitney test). Changes in PWV and other parameters

between the treatment and control arms over 6 months were compared for statistical difference.

In future analysis I plan to use linear regression models to determine the treatment effects adjusted for the pre- specified covariates (including gender, socioeconomic status, risk grouping (moderate or high) and number of time HAPPY London e-caching website used (number of log ins as a measure of dose). In a pre-specified sub-analysis, I will explore in each treatment group whether there was a change in PWV between baseline and 6-month follow-up using paired t-tests or non-parametric tests if data were not normally distributed.

Depending on the final results the aim was to conduct cost-effectiveness analysis for the short-term (clinical trial duration) and the long-term by extrapolation using decision analysis models.

A proportion of the baseline data was used as a control group for other clinical trials from our group, as part of a cross-sectional or case-control analysis. This was done following an amendment requested from the ethics committee to use the data in conjunction with other studies and also to perform spirometry measurements. The request was approved and we subsequently consented participants for this prospectively (see consent form in Appendix). Participants were asked to sign the amended copy of the consent form, at subsequent visits, if they had already completed the older consent form without this clause prior to ethics approval for the amendment.

Chapter 4 - Development of the HAPPY London Study website and how it works

Preamble

In this chapter I outline the process that participants need to go through during the study, with a particular emphasis on how this related to their use of the HAPPY London website and e-coaching tool. The HAPPY London website was produced in collaboration with the HAPPY Globally Foundation and their web team. The website information was previously produced in the Dutch language. For the purpose of the HAPPY London Study the web team and I redesigned the website to try and suit a study environment by adding in the researcher administration and participant summary page. I also tried to ensure that the information was relevant to the UK population. The web team translated the contents of the website and Dr Steffen Petersen and I checked the content for UK English spelling, grammar and conforming to the current medical knowledge and recommendations. I also helped to ensure that the contents of the personalised and generic email encouragements that participants received were relevant to the UK population.

Home page

In order to take part in the study all participants were required to visit the www.happylondon.com website. The main home page provided brief information about the aims of the study and steps required for those wishing to take part (Figure 6). Additional tabs provided further information about the study and what would be required to enrol. Inclusion and exclusion criteria, how to register details about the international HAPPY project was also provided. A 'Contact' page was available for any specific queries with the option of emailing the query from the website along with a contact number for the research team.

Participants had to register in order to complete a mini-check questionnaire to confirm if they met eligibility criteria. Once registered participants were able to log into a personal account. For those in the e-coaching treatment arm this provided personalised information based on results of self-completed questionnaires and

results from the screening visit. Access to the lifestyle and other questionnaires was available for completion by all participants randomised into the study. For those in the SOC treatment arm the webpage provided dates and times of all appointments booked for them during the study.

Figure 6. Home page and website registration information

Registration was relatively simple and required a valid email address and the name of the participant in order to make the website personalised (Figure 7). Once registration details were submitted, an activation email would be sent to the email address to confirm correct email functioning. Participants were also warned to check their junk mail in case their filter deemed it as such.

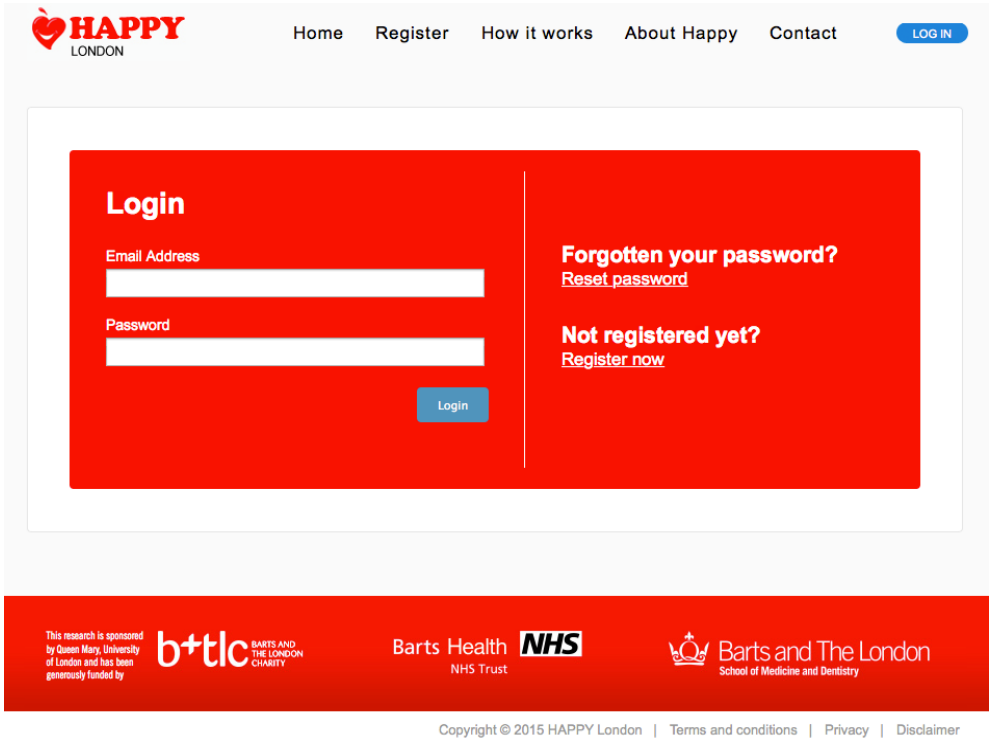


Figure 7. Registration and log in link

"About us"

The 'About us' page provided information about the hospital trust and also about the HAPPY globally foundation and the work that they do so as to inform participants of the parties involved in the study (Figure 8)

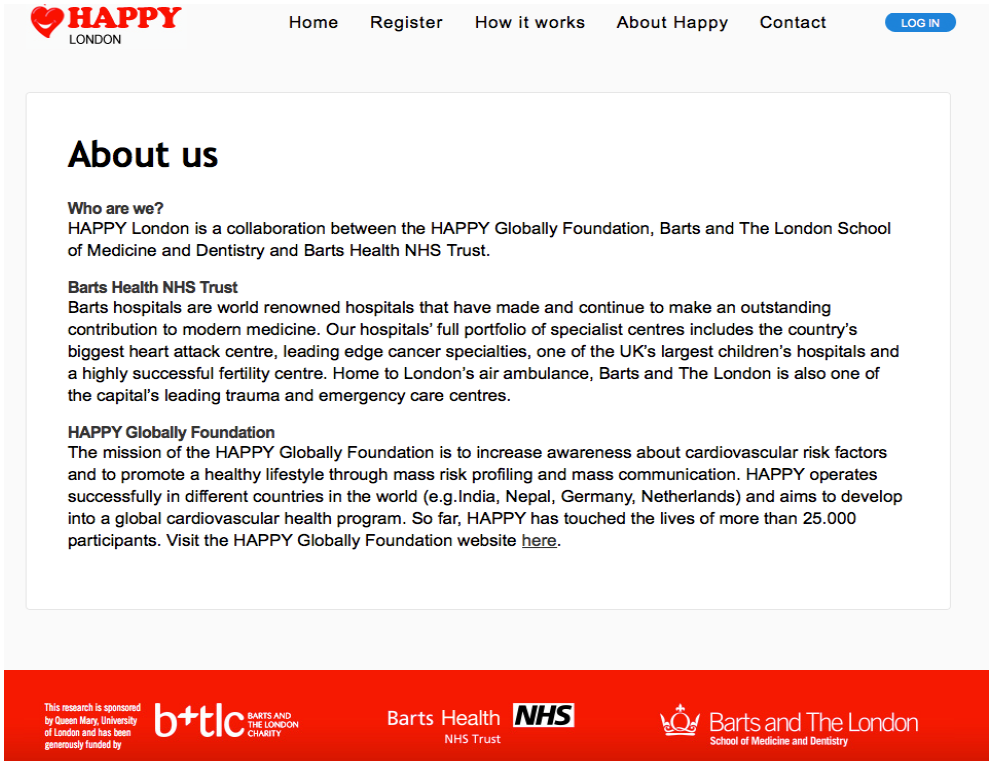


Figure 8. 'About us' page

How it works page

Potential participants were informed in advance of the inclusion and exclusion criteria and what they needed to do to enrol for the study (Figure 9). Previous CVD was an exclusion criterion in view of the primary prevention nature of the study. The steps in the process were outlined and it is also mentioned that eligible participants would have access to their information on-line information in the group randomised to e-coaching. They were informed that a 'mini-check' questionnaire was required in order to check eligibility and to provide an initial estimate of future CVD risk.

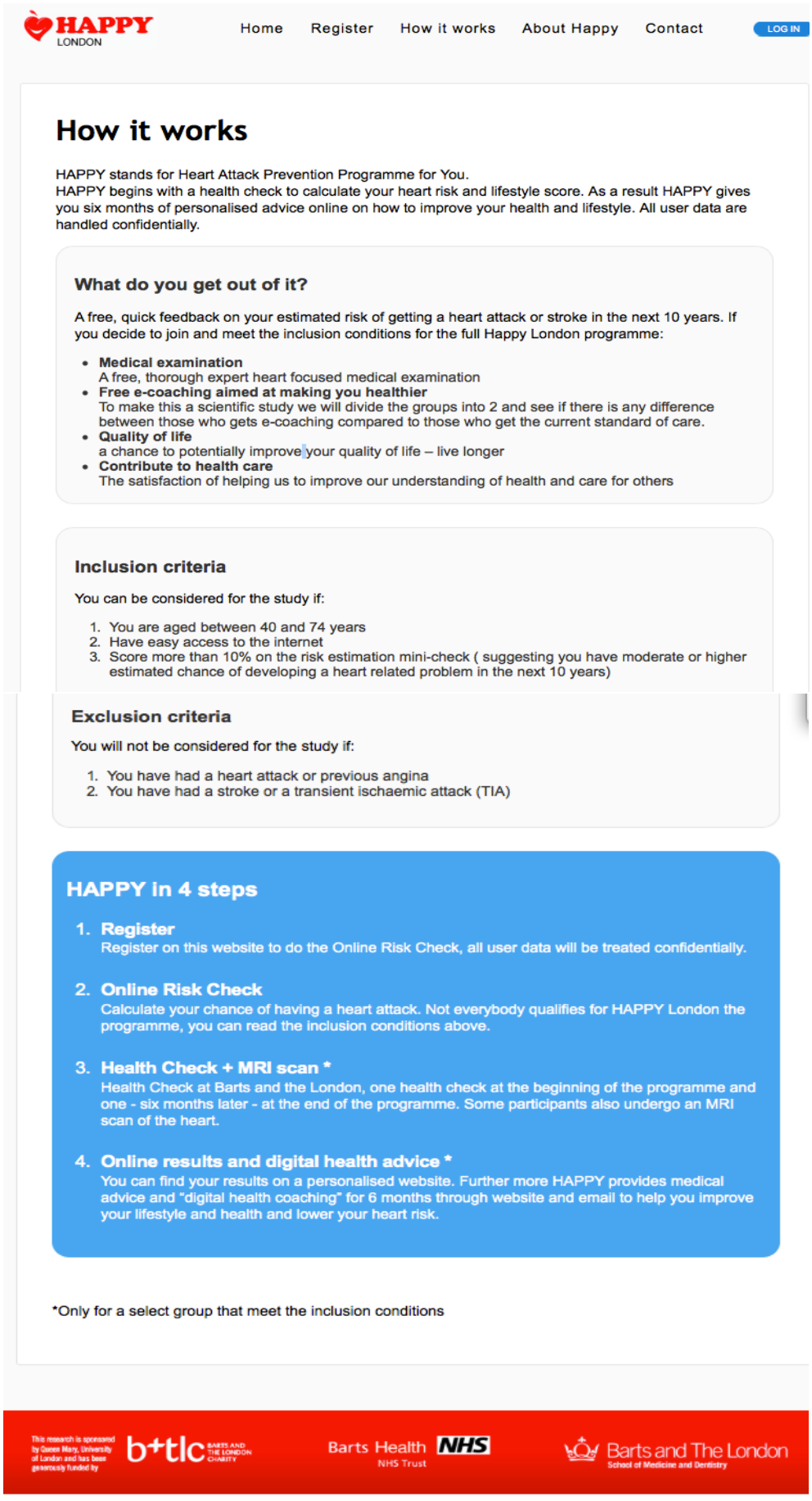


Figure 9. How it works page

Contact page

The 'contact' page allowed potential participants to contact the team regarding technical issues about the website or queries about the study (Figure 10). Technical issues usually would be dealt with by the web team and other study queries and concerns would be dealt with by the research physician or nurse.

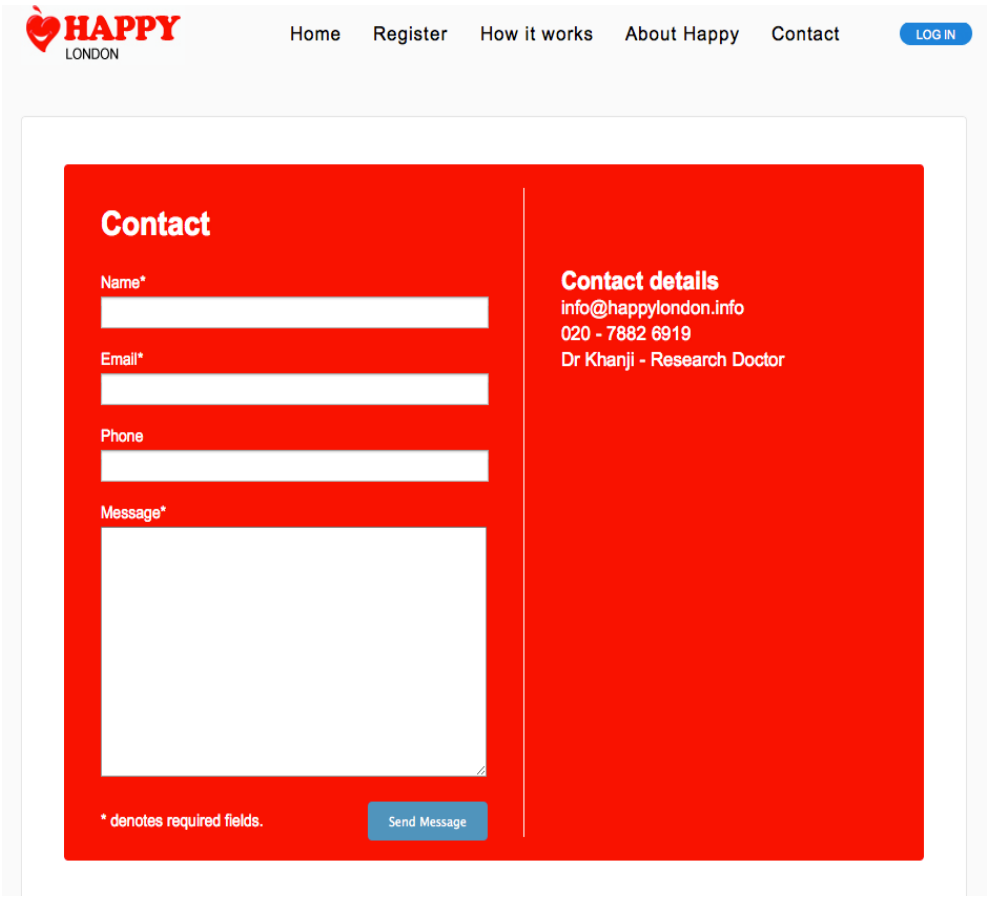


Figure 10. Contact page

Mini-check questionnaire

Once the mini-check questionnaire was completed, they were given information about their estimated 10-year CVD risk group. If this was below 10% they were informed that they did not meet the risk threshold requirement. If it was above 10% then they were invited to attend the screening visit (Figure 11). They were also informed that if they decided not to take part in the study then they should contact their GP for further assessment to confirm CVD risk level and any treatment or advice that may be required.

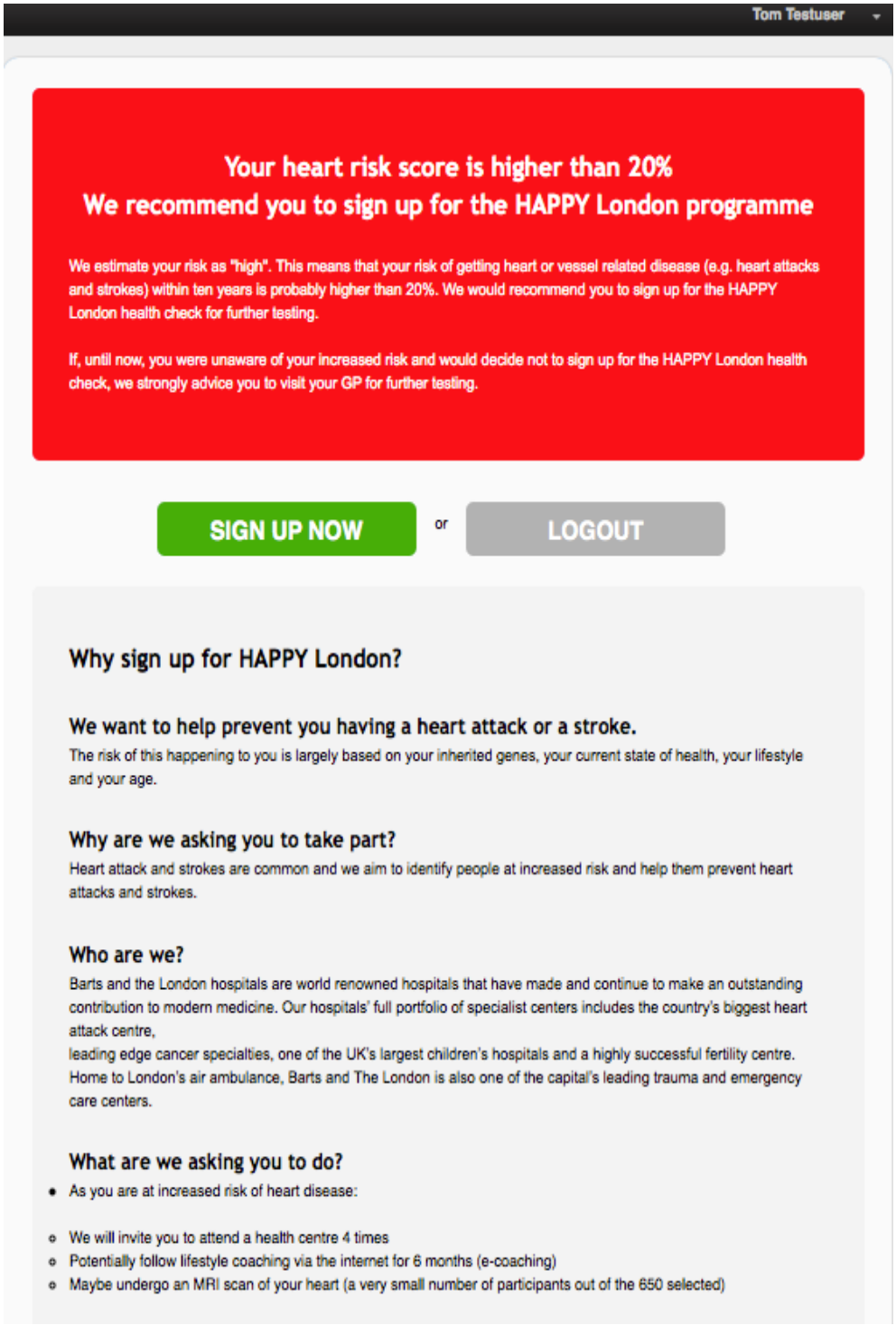


Figure 11. Result of the mini-check questionnaire with risk estimate

Booking an appointment for screening visit

Once participants completed the 'mini check' questionnaire and they were deemed potentially suitable based on eligibility criteria, they were presented with the option to sign up for the study and choose the visit date for the physical screening visit (Figure 12). If they chose to join they were provided with an online booking

calendar with available appointment slots (Figure 13). The personal information of the participant was obtained in a secure web environment in order to make the website and emails personalised. Telephone contact details were also obtained for appointment communication purpose.

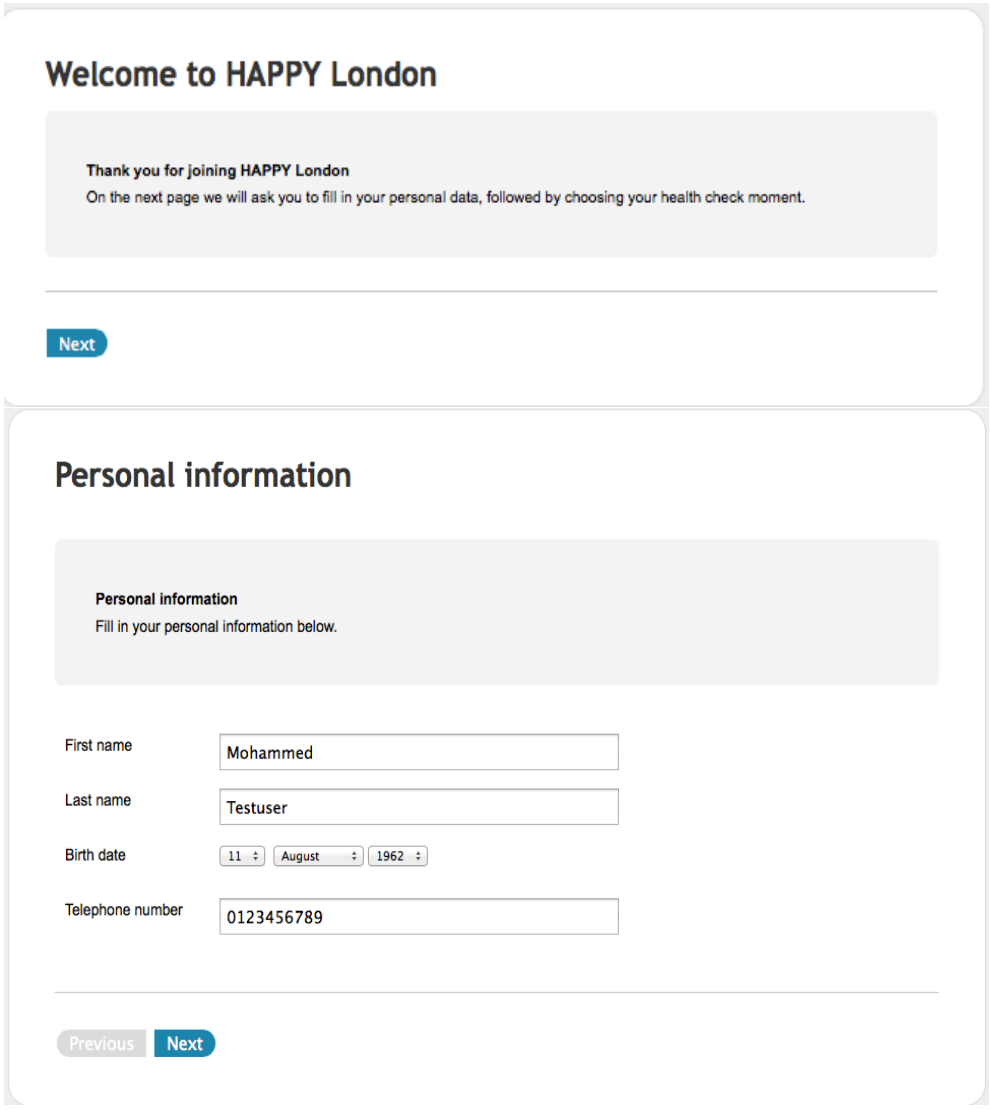


Figure 12. Personal information page prior to booking appointment

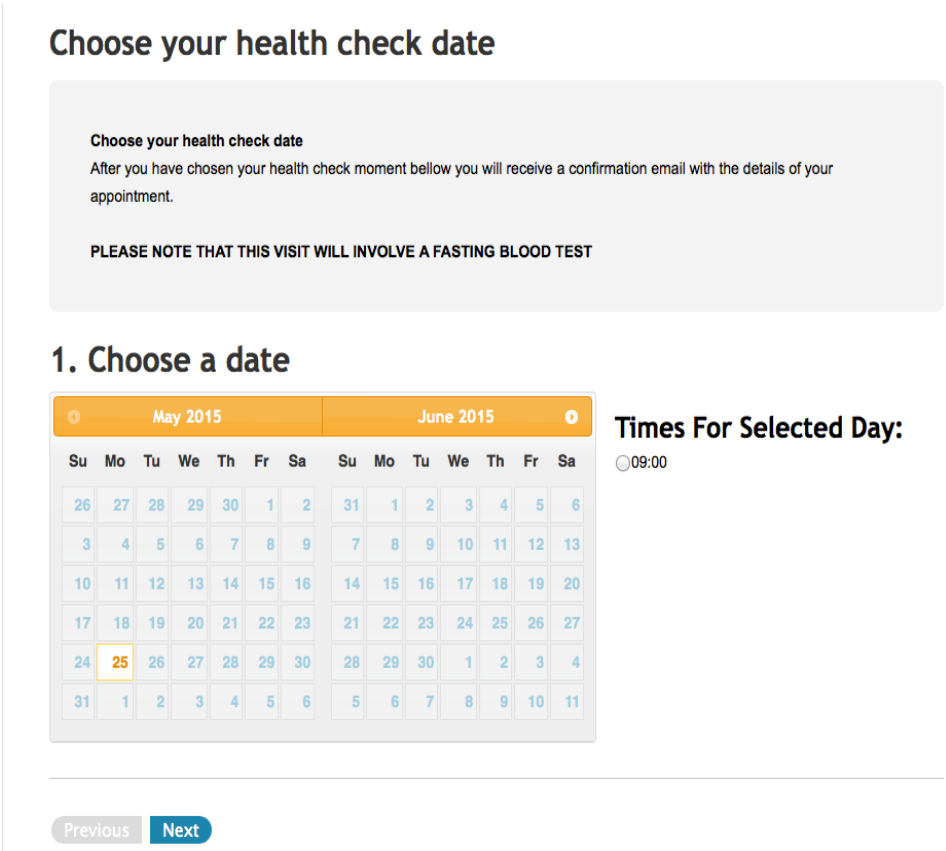


Figure 13. Appointment booking system

Screening visit information

Once the appointment slot was selected they were given a summary of what to expect at the first visit and the address of the research unit on the website page (Figure 14). They also received an email confirming these details with attachments that included the study PIS, a copy of the consent form that they would be asked to complete at the visit, a map of the venue with directions for travel. Participants that were potentially eligible for CMR scans also received the MRI safety questionnaire. This safety questionnaire was completed with the research nurse/doctor on the day of attendance along with the consenting process.

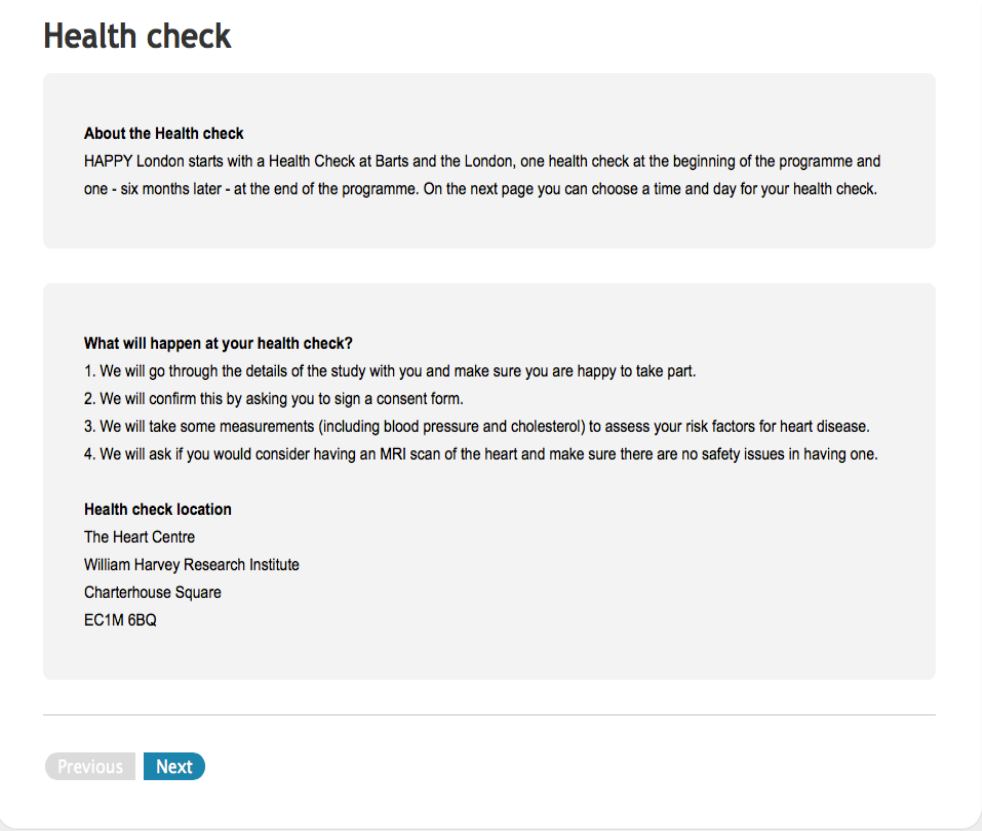


Figure 14. Information on what to expect at the first visit

Following screening visit (visit 1)

Risk factor profile and measurements from the screening visit were entered onto the website via the nurse log in page. This included BP, weight, BMI and smoking status. Blood test results such as cholesterol and glucose were automatically transferred to the www.happylondon.info website from the laboratory within 24 hours. This information enabled calculation of the QRISK2 score. If QRISK2 score was 10% or more the participant was deemed to be eligible for randomisation.

Once randomised participants were sent an email with the 2nd visit appointment, which would have provisionally been booked at the first visit. All participants were asked to complete a lifestyle questionnaire. For those randomised to e-coaching they got this combined information to view from their home page. (The home page provided a summary score of the participants lifestyle and heart risk score (Figure 15). The home page also provided summary data of the progress of the participant's s lifestyle scores over the study period from baseline, 3-months and 6-months questionnaire data.

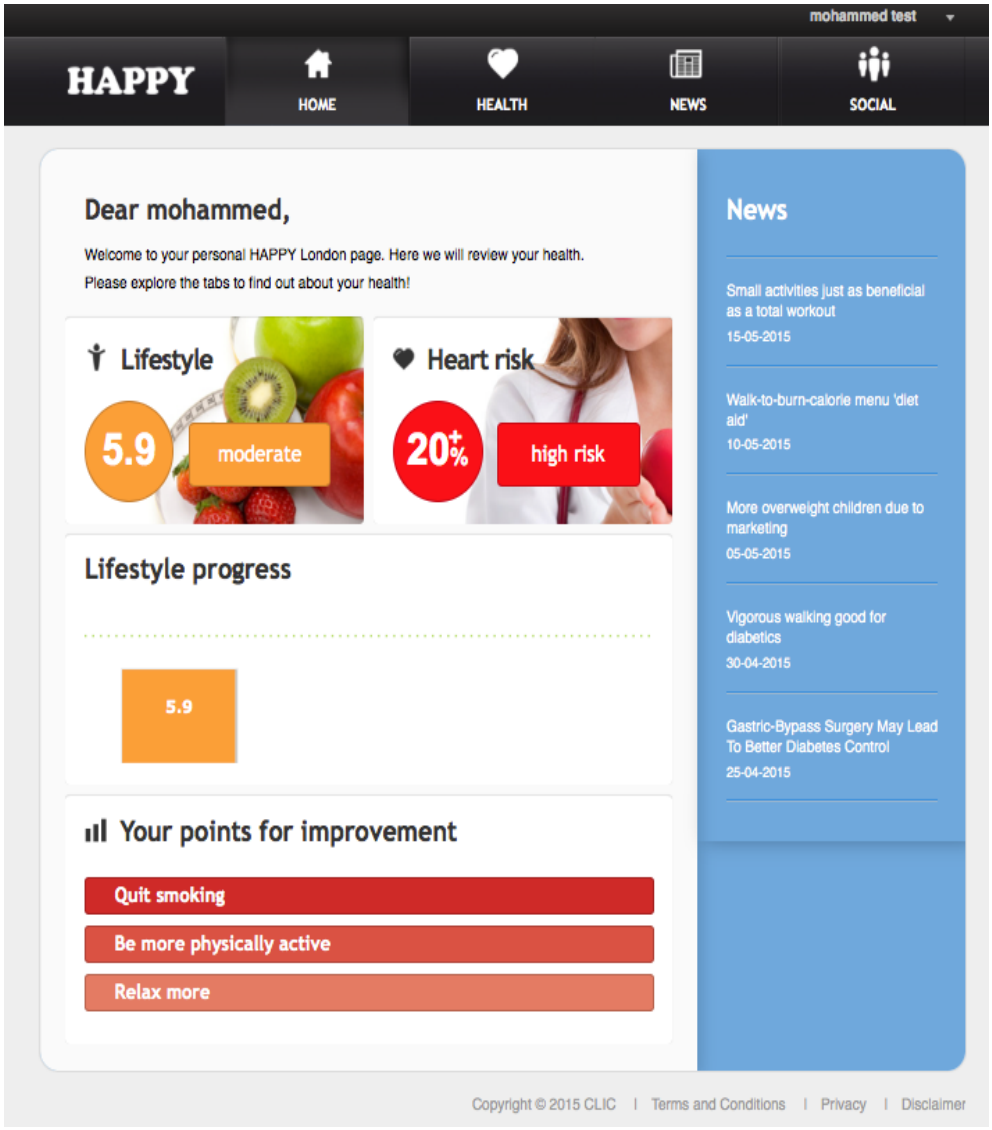


Figure 15. HAPPY London e-coaching home page

Lifestyle progress page

This provided a colourful summary of the lifestyle factors in the form of heart shapes. Green smiley hearts represented factors that were within the recommended range. Orange hearts represented borderline factors and red sad hearts represented suboptimal factors that should be addressed. It was recommended that participants aim to get as many green smiley hearts over the study period as possible, as their personal targets. At subsequent visits these were updated based on the 3-month and 6-month lifestyle questionnaires and the BMI as measured a by the research team. A summary score of the lifestyle factors is calculated for each participant based on the combination of lifestyle factors

highlighted in the lifestyle section with the best achievable score of 10. On the website a score of above 8 was deemed to be very good gave a green bar, between 6 and 8 an orange bar and less than 6 a red bar, suggesting need for significant improvement. The aim for the participant was to get as close to the highest score possible of 10. The first column showed the results available after the first visit from the baseline lifestyle questionnaire (Figure 16).

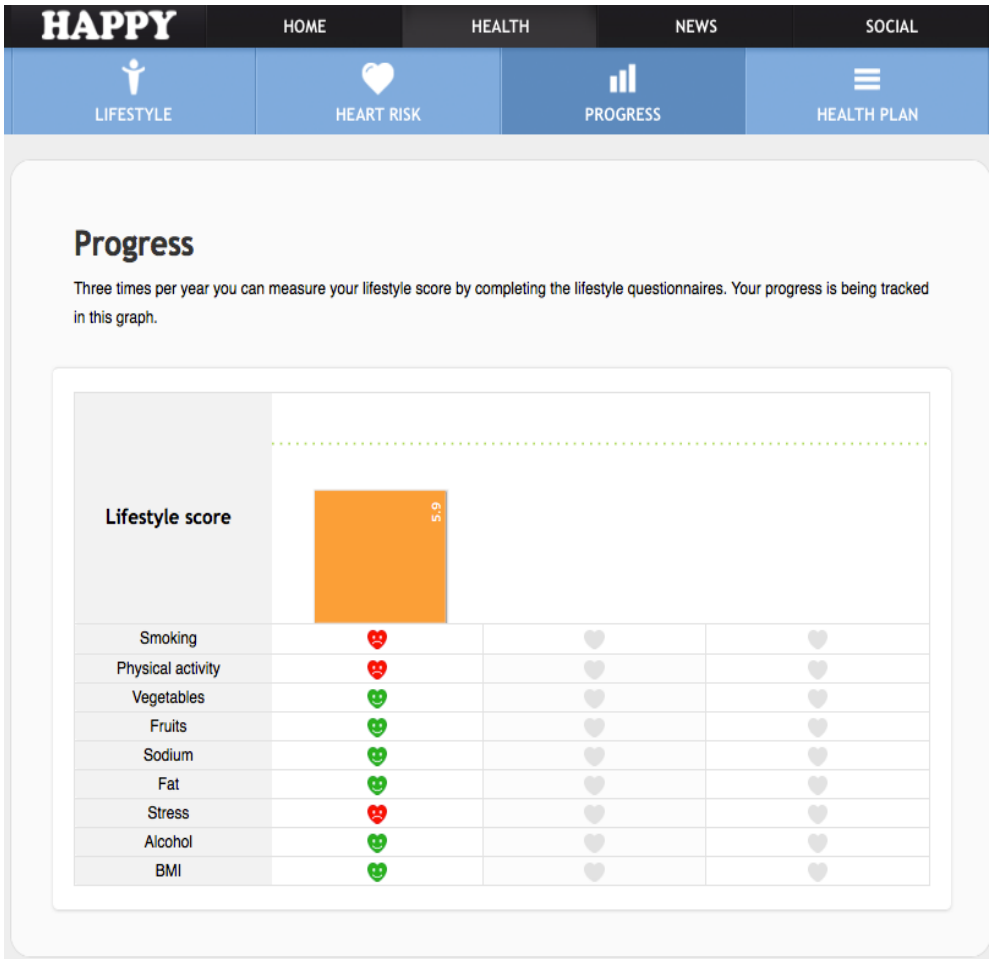


Figure 16. Lifestyle progress page

Figure 17 is an example of a participant that had come to the end of the study and shows the baseline, 3-month and 6-month progress with a gradual improvement seen. Participants could thus have a summary of which points they had improved on to encourage them to maintain these and also which factors may still require further attention.

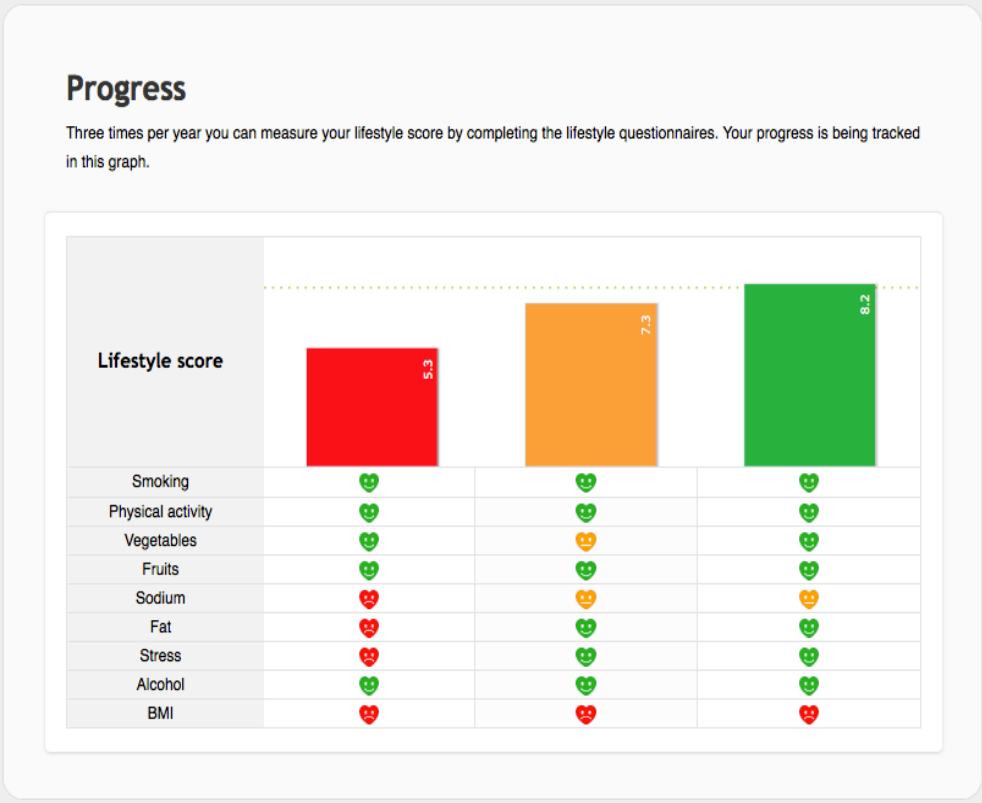


Figure 17. Lifestyle progress page for someone completing the study

Settings page

The settings page allowed the participants to change their preferred name, which emails they wished to receive and the option to unsubscribe from the study if they wished to withdraw from the trial (Figure 18).

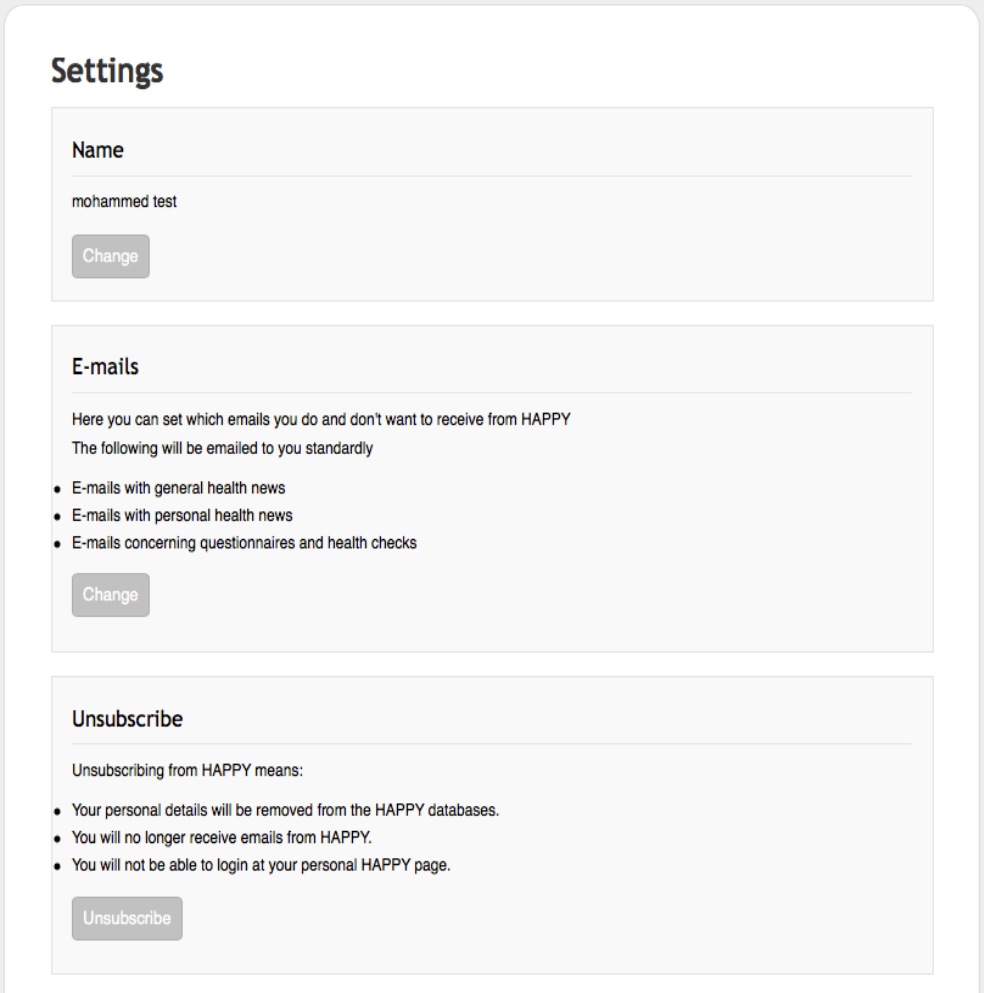


Figure 18. Settings page

Questionnaires

Participants were asked to complete the questionnaires prior to the 2nd, 3rd and 4th visits. These were available after logging onto their page as a yellow box with a message asking them to complete the appropriate questionnaires during various pre-specified periods during the study. Alternatively, questionnaires could be found by going to the 'settings' tab. The section labelled 'Questionnaires' provided all the questionnaires that needed completing for the visit (Figure 19). Prior to having had access to their home page results participants in the e-coaching group were required to complete the lifestyle questionnaire that would allow generation of their personalised results. The data from the first visit including the blood test results, BP and estimated CVD risk score was also available based on the input data from both the participant and the study team. The questionnaires were also

available for the SOC group. However when they logged onto the website the only other information that was available to them was the schedule of future visits.

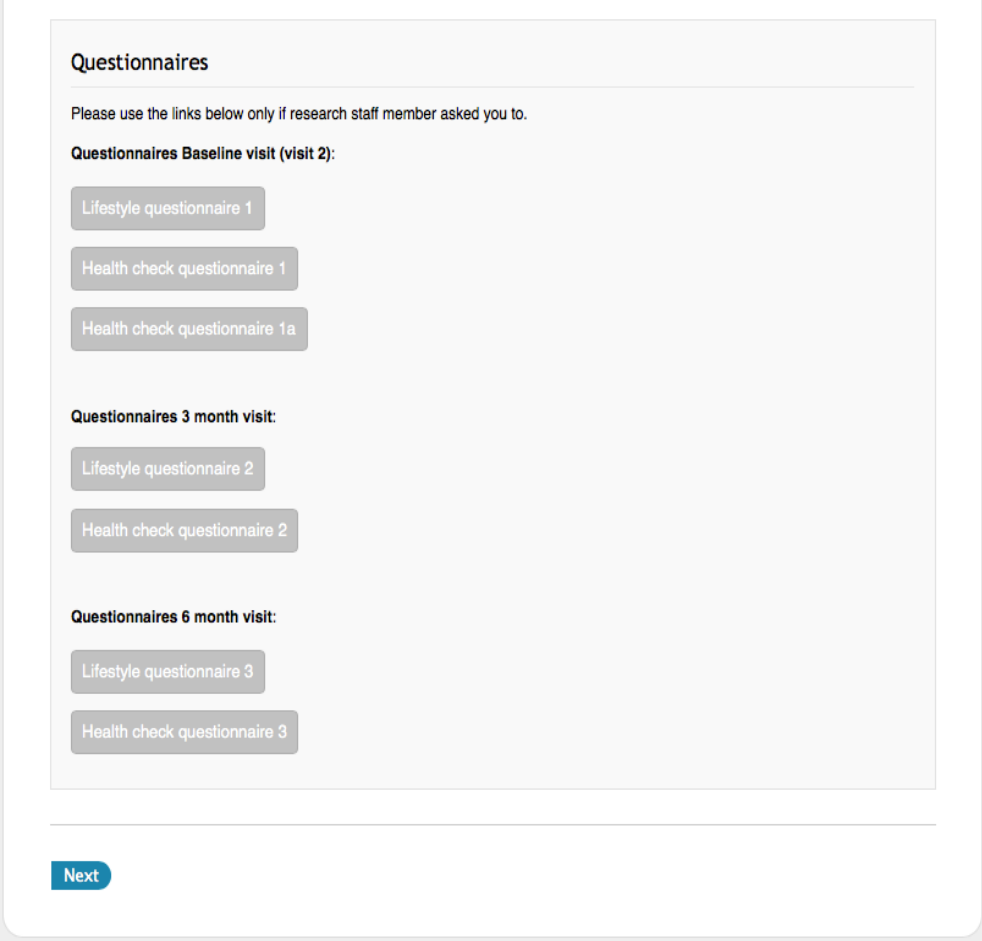


Figure 19. Questionnaires requiring completion during the study period

General health news items

News items based on recent studies or topical issues in the media pertaining to primary prevention were updated approximately twice weekly. This aimed to provide short generic information to encourage general healthy living (Figure 20).

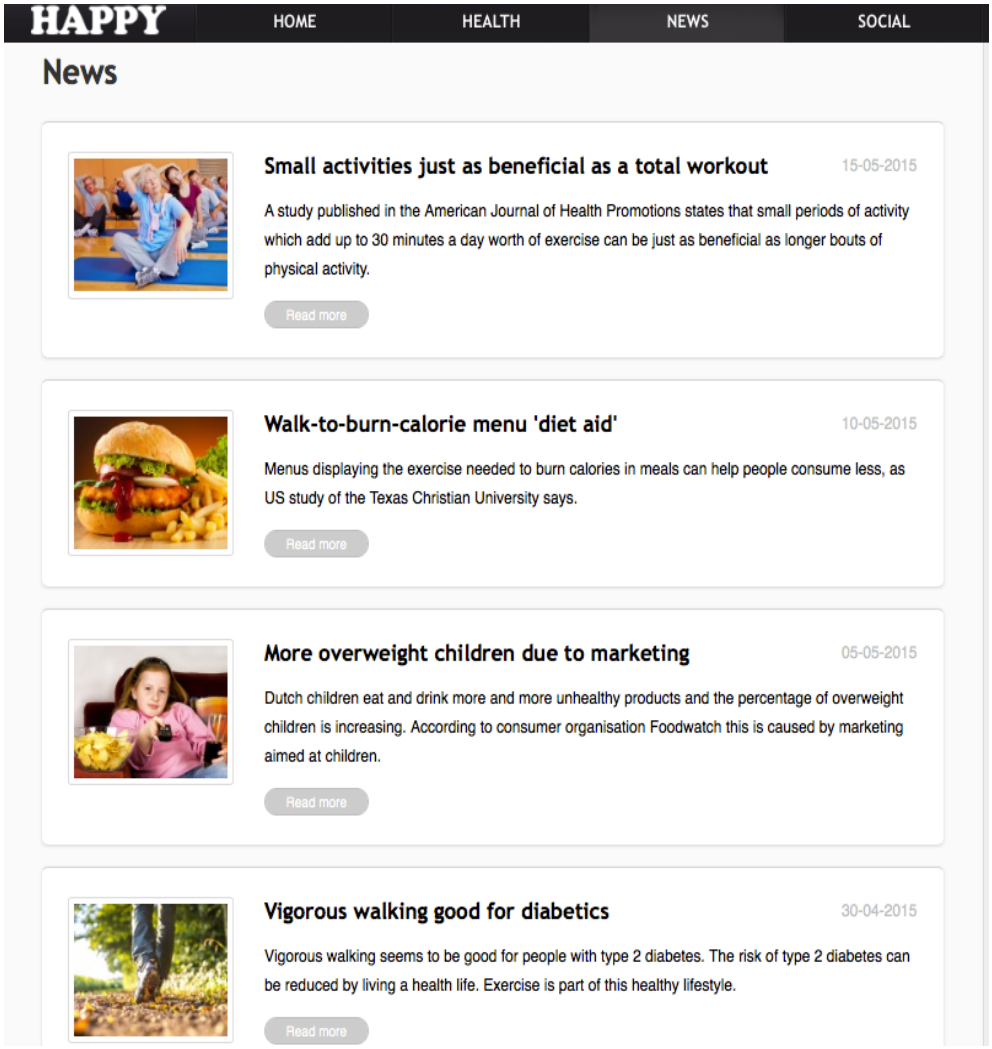


Figure 20. General news items

The health plan page

This formed one of the main components of the web page. It provided a tailored plan for each individual based on the factors that were deemed to be suboptimal and that the participants were encouraged to improve on (Figure 21). These factors also formed the main points that would be discussed on a face-to-face basis with participants as they highlighted the factors that were identified from the lifestyle questionnaire or from the risk factor assessment at the first visit.

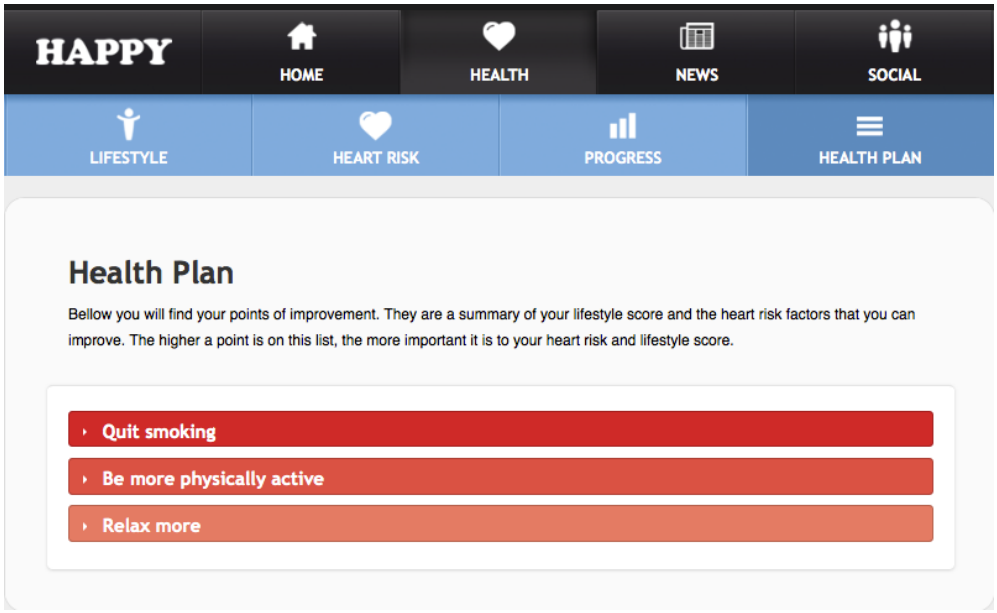


Figure 21. Health plan page

Clicking on each health plan item opened up further boxes with more information about that factor including what the participants result was, what the ideal result would be and further information about that particular risk factor and ways of improving over the study period. This page aimed to improve participants understanding of the importance of the risk factor and its relationship to future CVD complications. It also provided links to other websites that provided further information or support links such as the NHS choices website (http://www.nhs.uk) and links to short motivational and informative videos on that topic. The example below advises on quitting smoking, being more physically active and trying to reduce stress levels by providing relaxation technique options (Figure 22, Figure 23 and Figure 24).

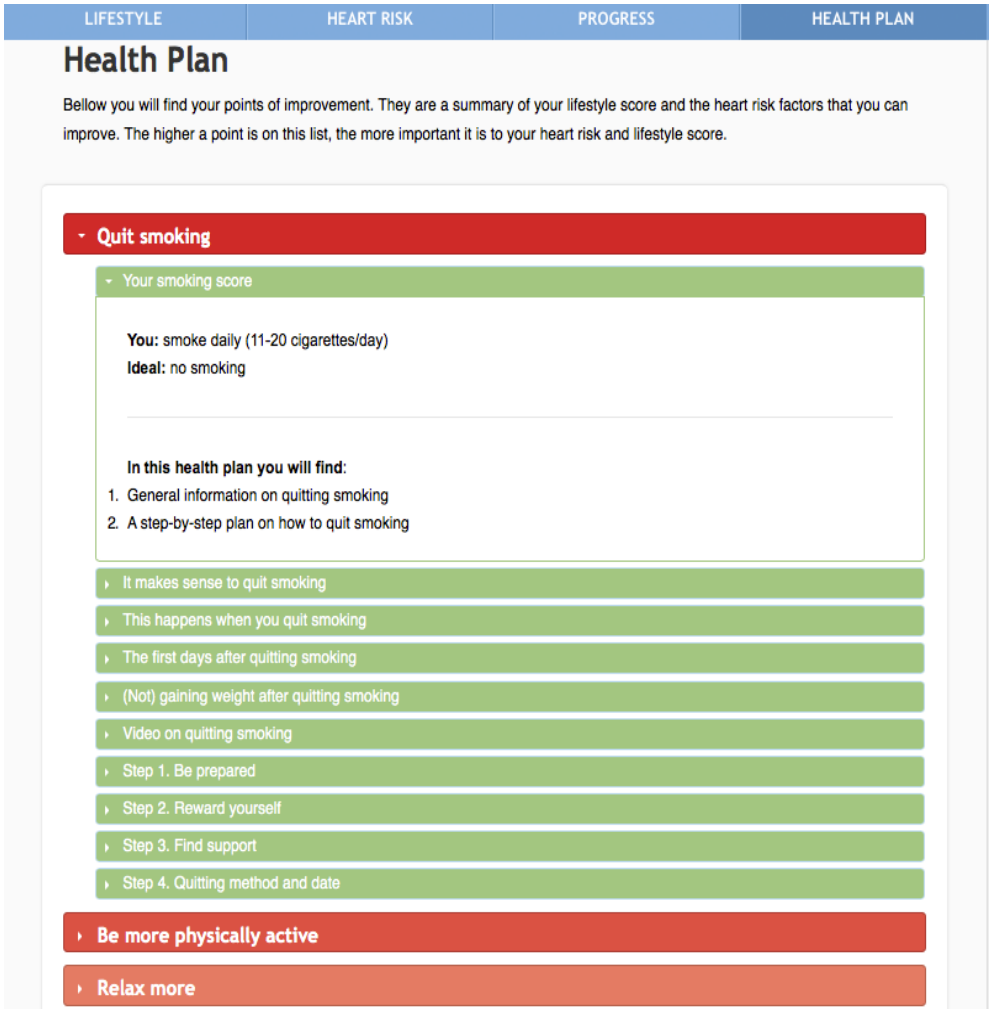


Figure 22. Pop-up box in health plan item 'quit smoking'

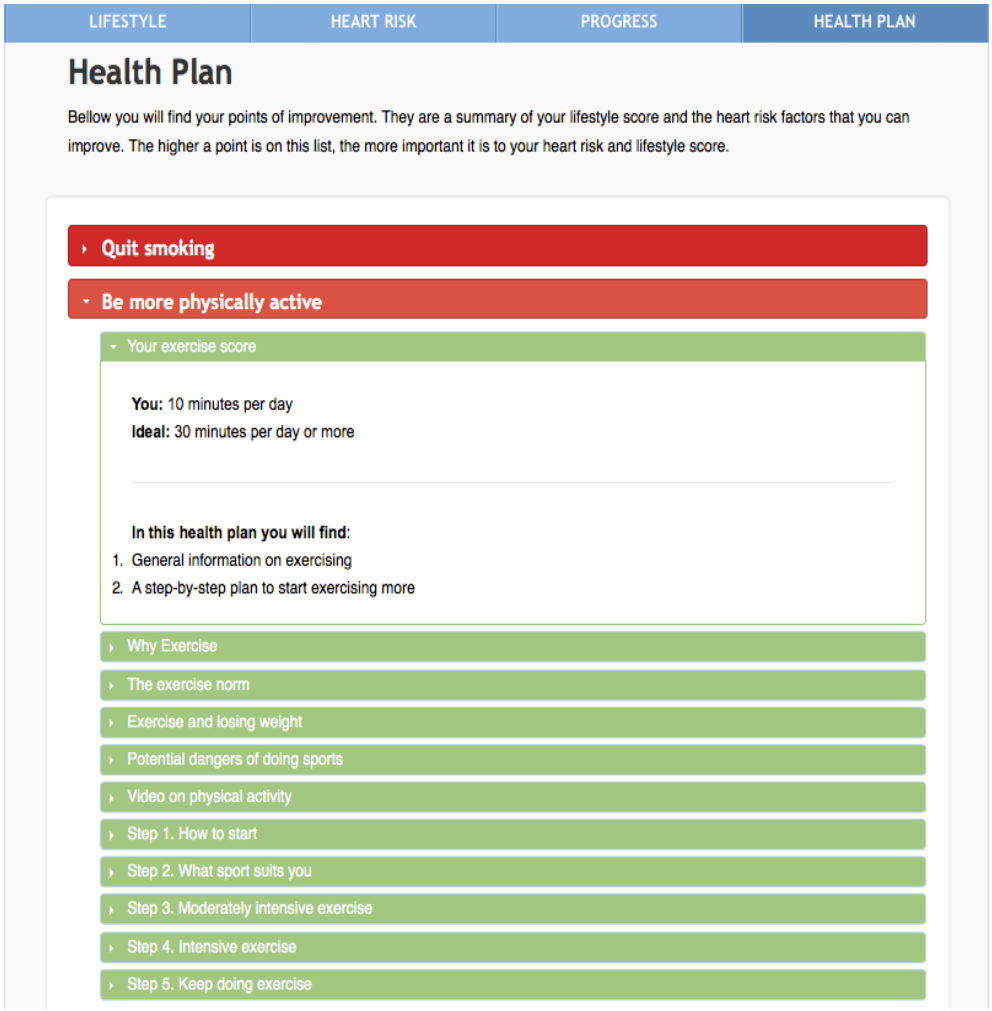


Figure 23. Pop-up boxes with more information on health plan item 'be more physically active'

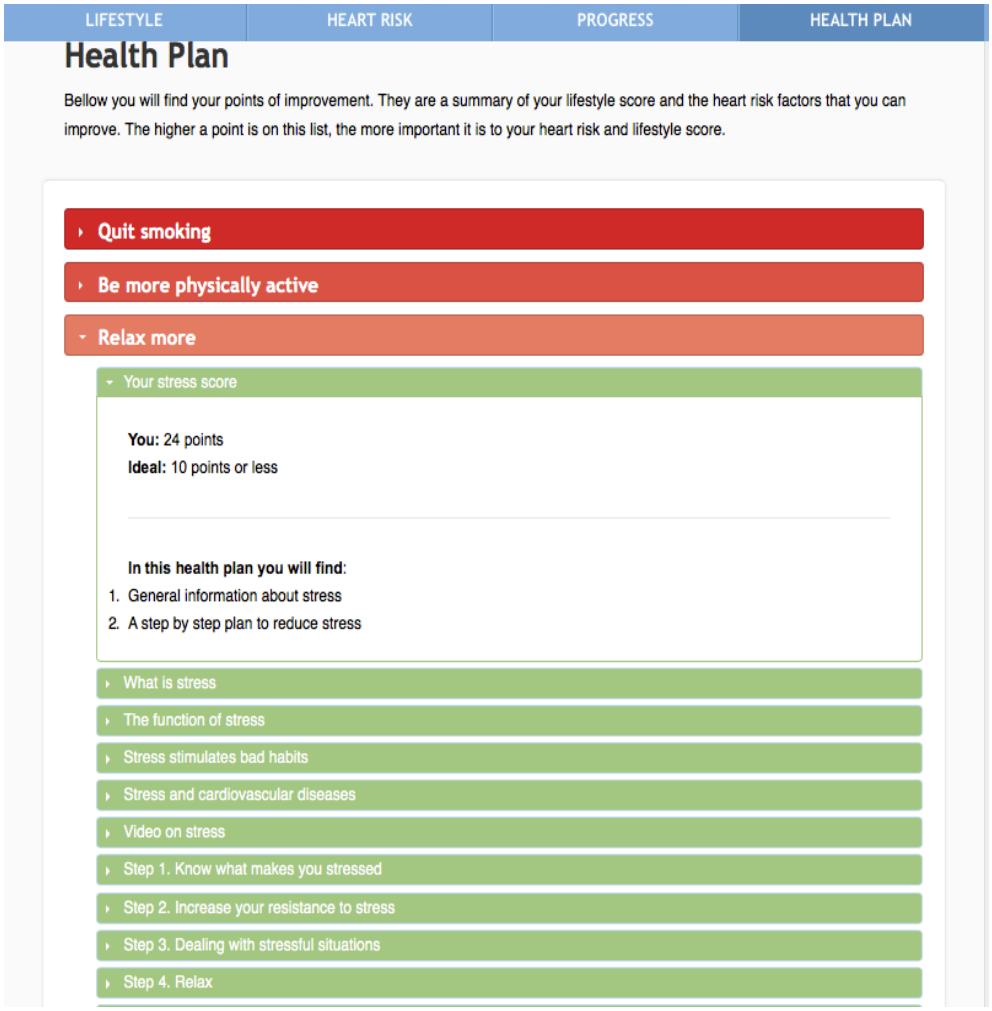


Figure 24. Pop-up boxes with more information on health plan item 'relax more'

Heart Risk page

This page provided a colour coded summary of the participants estimated 10-year CVD risk and the common CVD risk factors including hypertension, diabetes, cholesterol, age and family history (Figure 25). There was also an explanation of cut-off thresholds used for the labelling of mild, moderate and high CVD risk based on cut offs used at the time of the study.

Due to the age criteria for the study, participants of middle or older ages were informed of the impact of age on CVD risk in order to encourage them to address the modifiable risk factors. The same was mentioned where they may have had a family history of premature coronary artery disease ('hereditary'). Using the same colour coding a green happy heart represented factors that were within the

recommended ranges from the guidelines. Orange heart symbols represented borderline or mildly elevated risk factors and sad red hearts represented suboptimal factors that should be actively addressed, particularly if reversible such as BP. Clicking on each of the factors on the heart risk page opened up further information links on BP, cholesterol, glucose levels, diabetes, age and hereditary factors (Figure 26, Figure 27, Figure 28, Figure 29, Figure 30 and Figure 31, respectively.)

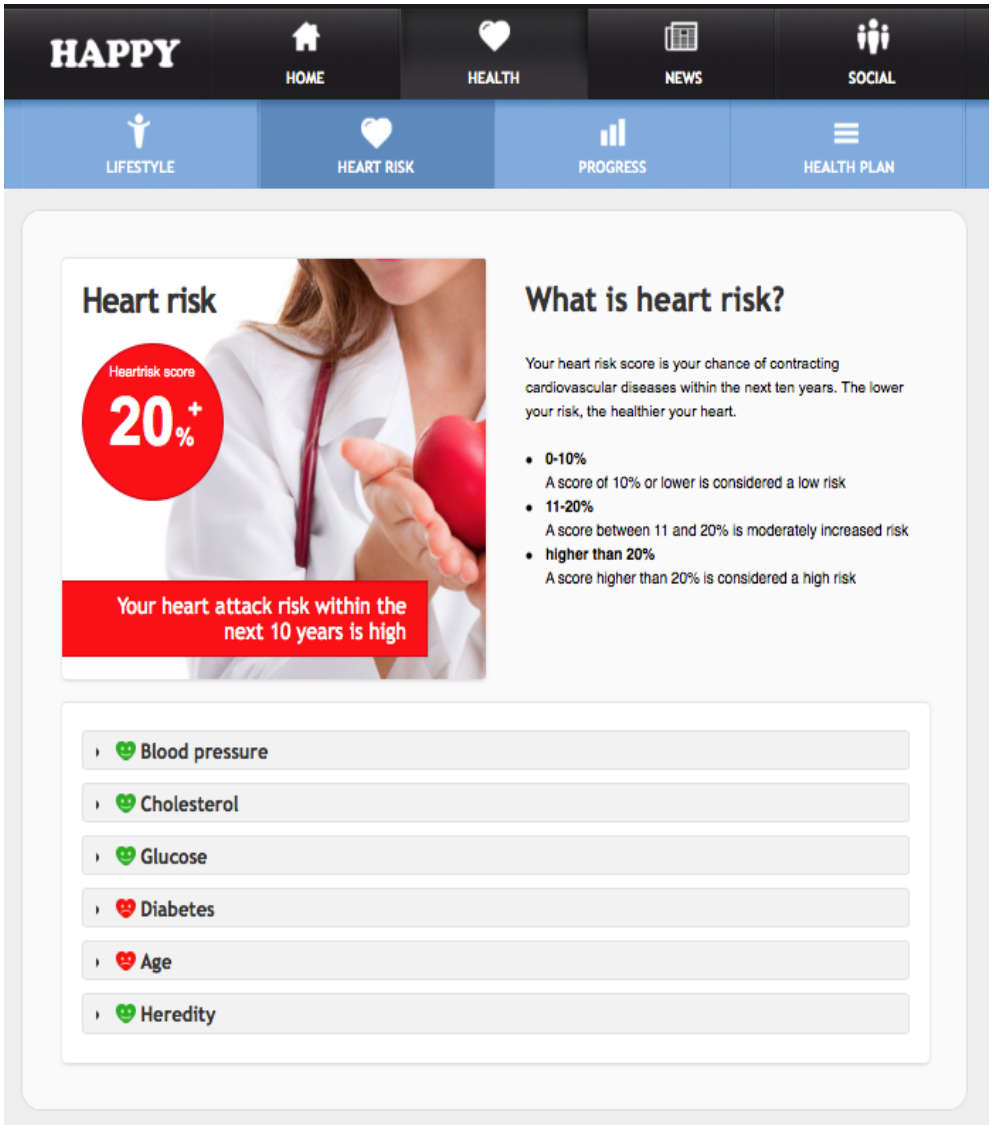


Figure 25. Heart risk page

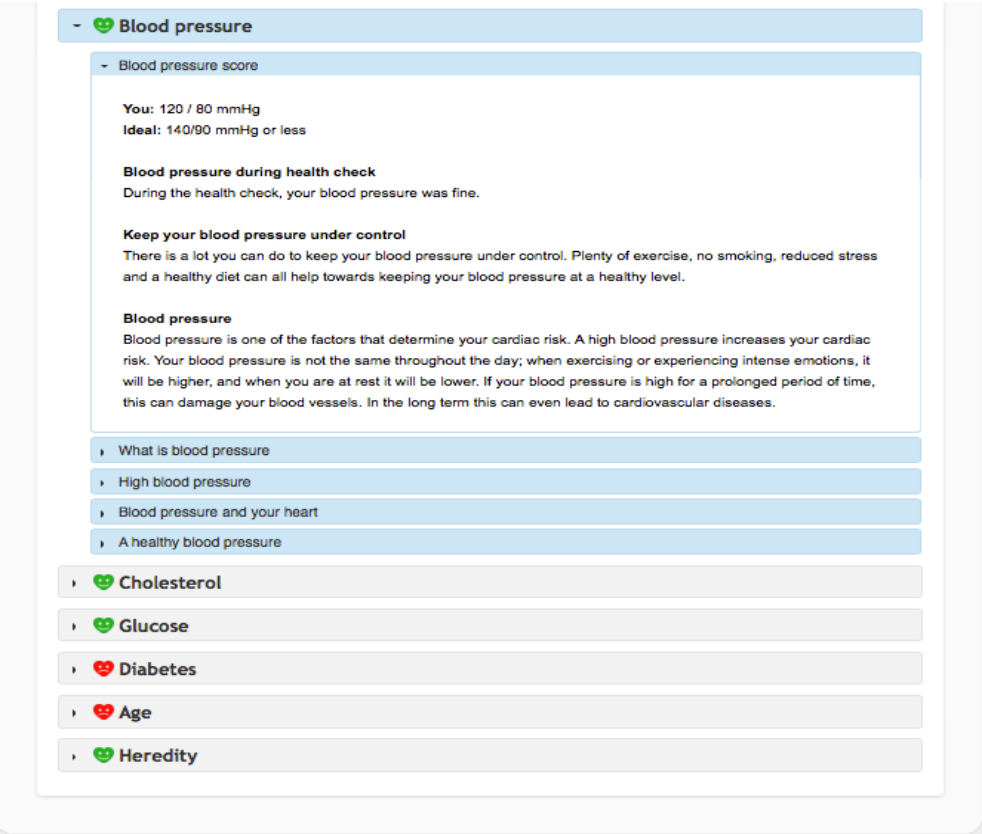


Figure 26. Pop-up boxes on heart risk page with more information on blood pressure

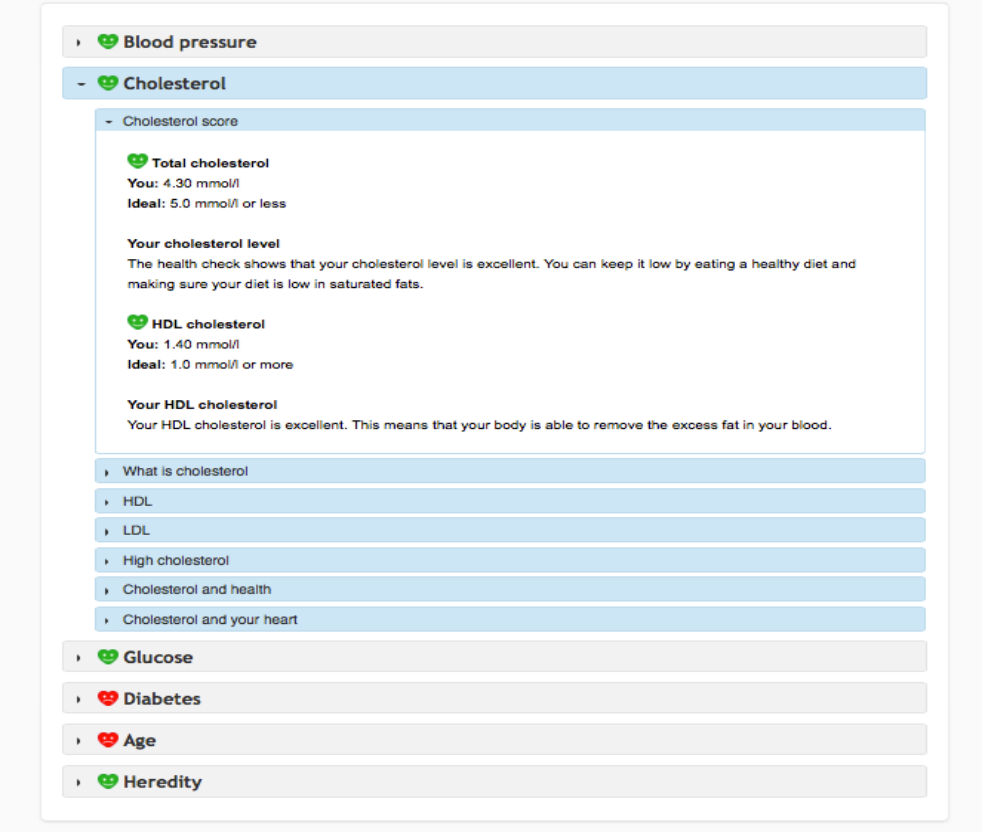


Figure 27. Pop-up boxes on heart risk page with more information on cholesterol

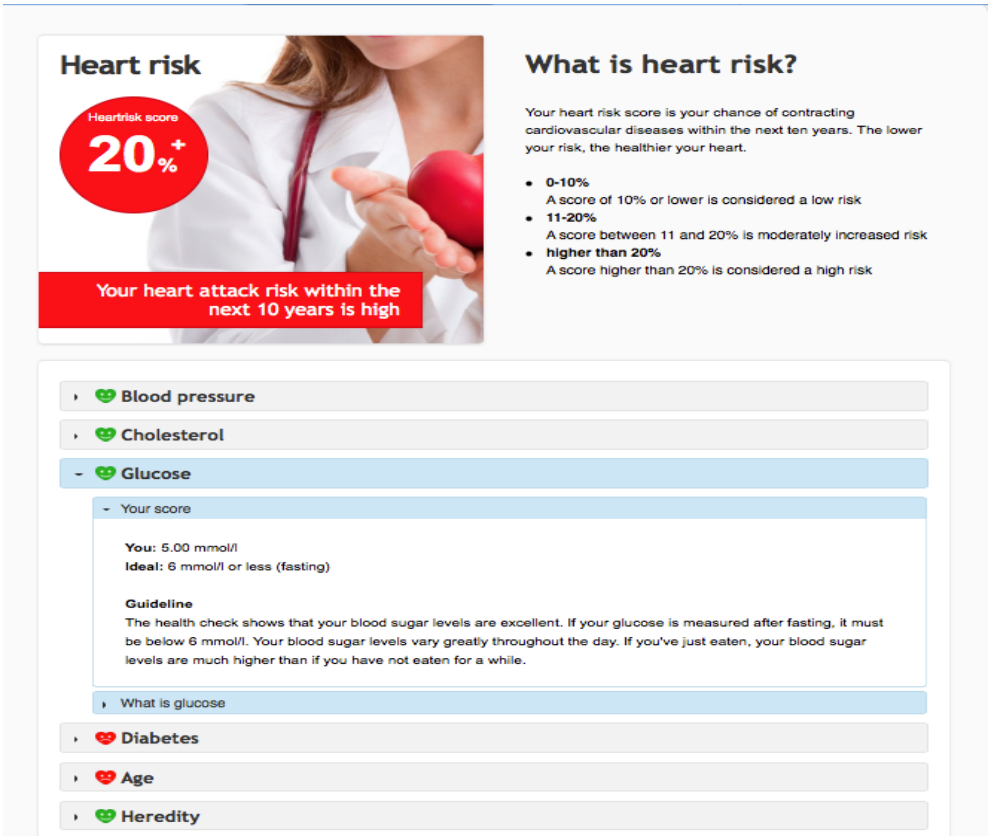


Figure 28. Pop-up boxes on heart risk page with more information on glucose

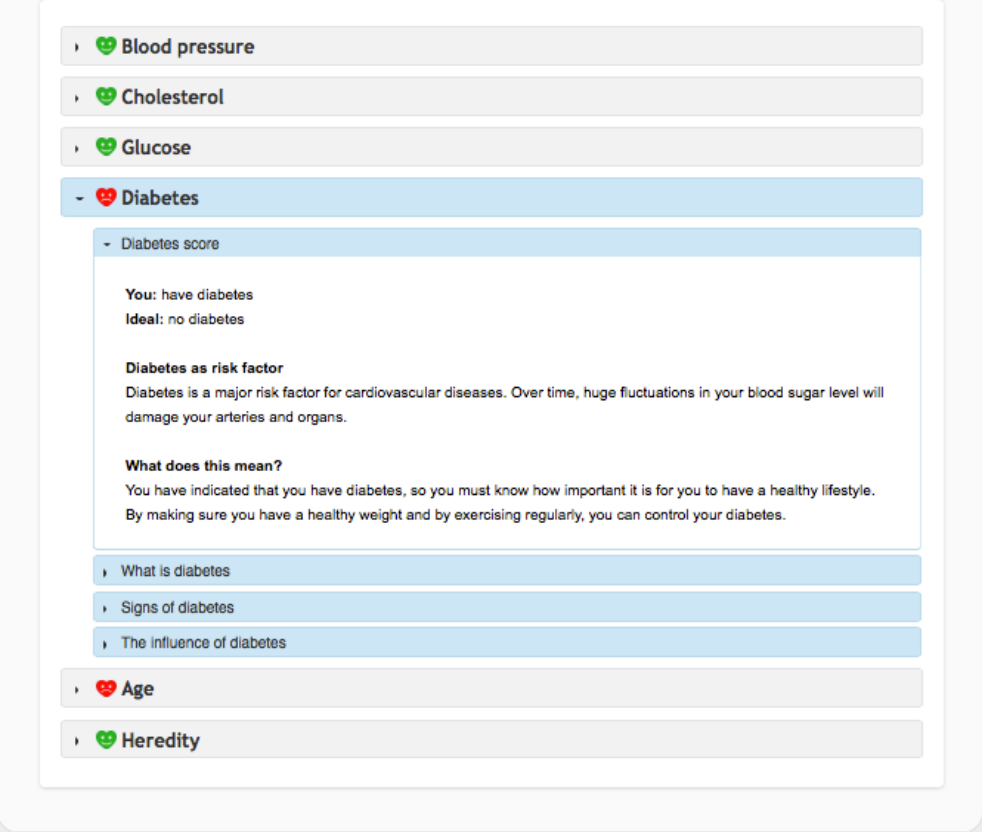


Figure 29. Pop-up boxes on heart risk page with more information on diabetes

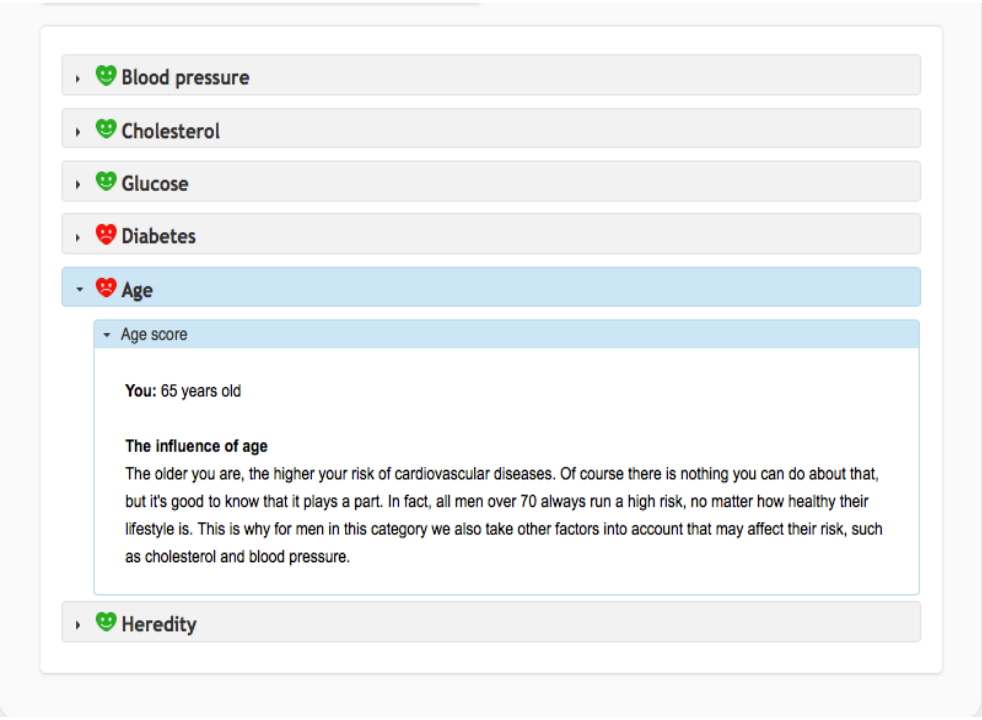


Figure 30. Pop-up boxes on heart risk page with more information on age

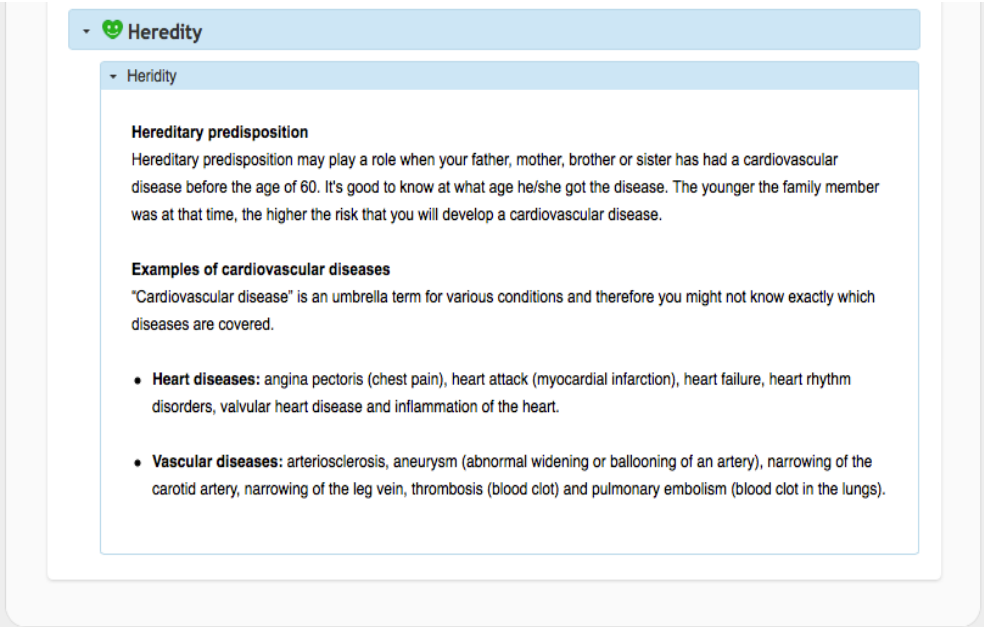


Figure 31. Pop-up boxes on heart risk page with more information on hereditary factors

Lifestyle factors page

This page provided a colour-coded summary of important factors related to lifestyle. An overall lifestyle score was given for all the factors combined and an explanation of the thresholds used for grading lifestyle scores (Figure 32). Further information for each of the factors was provided by clicking on the black arrow for smoking, physical activity, nutrition, stress, alcohol and BMI (Figure 33, Figure 34, Figure 35, Figure 36, Figure 37 and Figure 38, respectively)

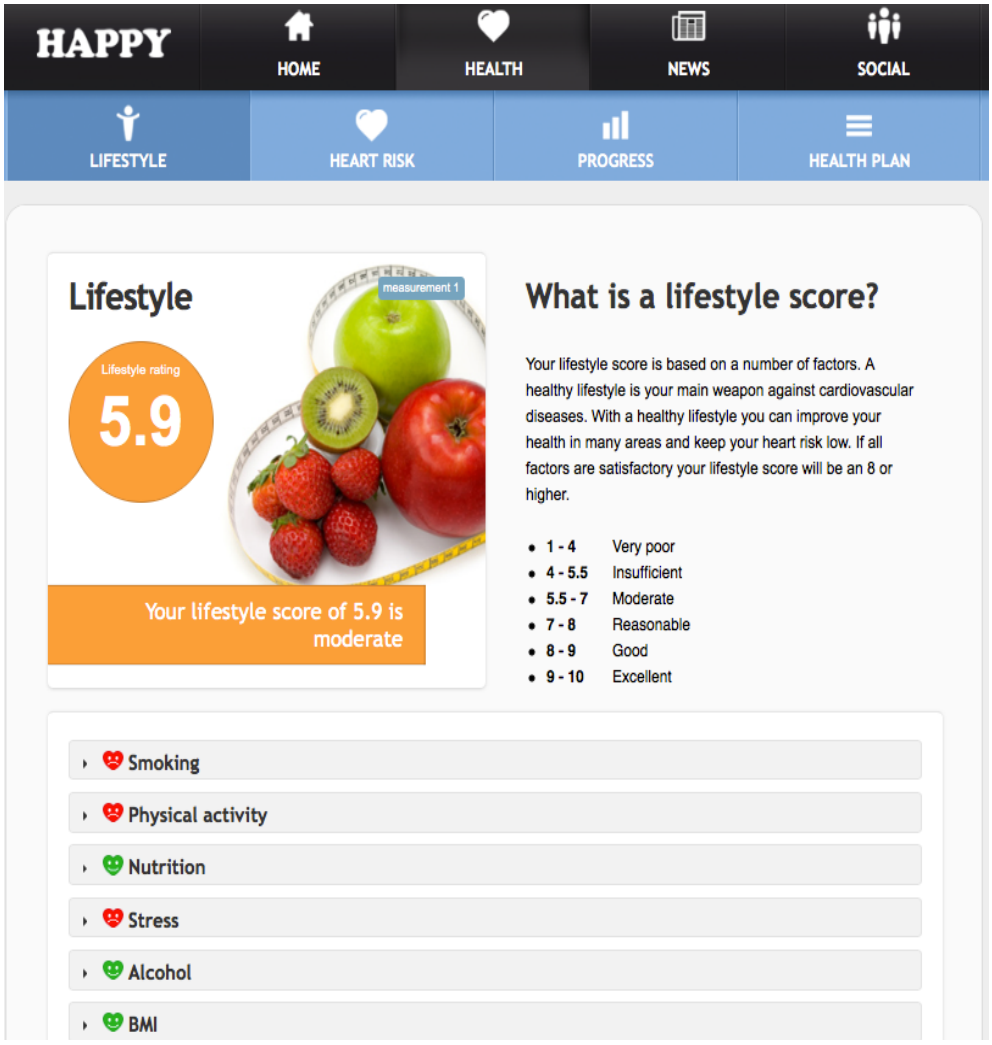


Figure 32. Lifestyle page

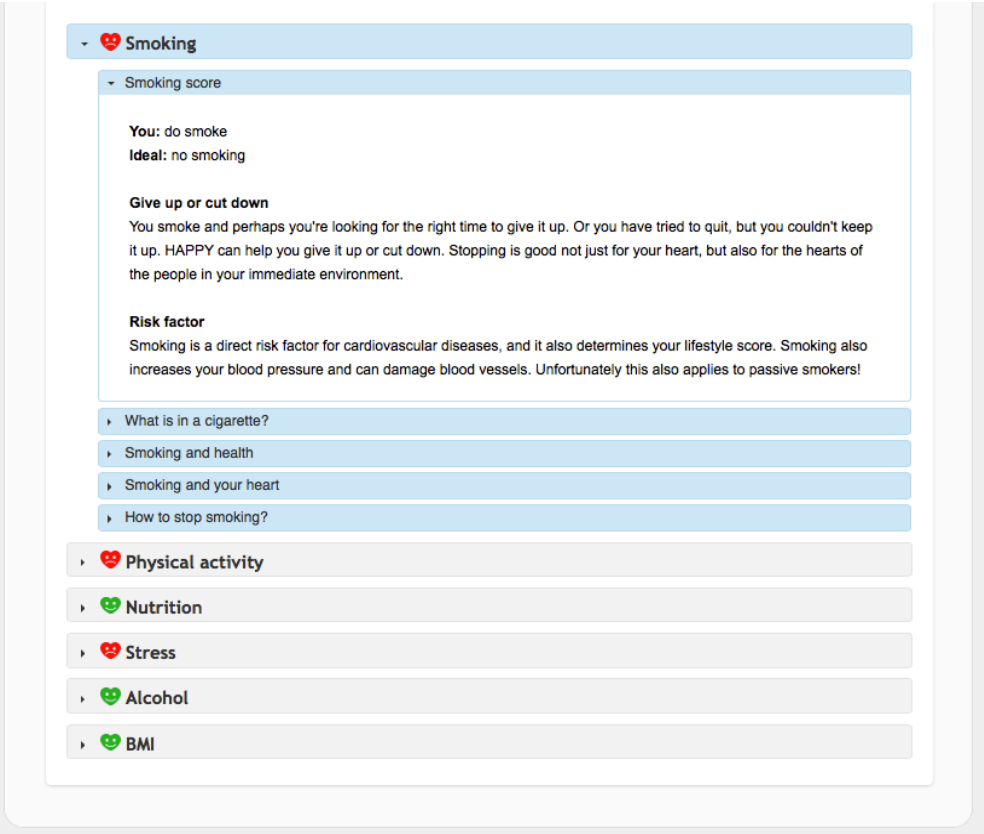


Figure 33. Pop-up boxes on lifestyle page with more information on smoking

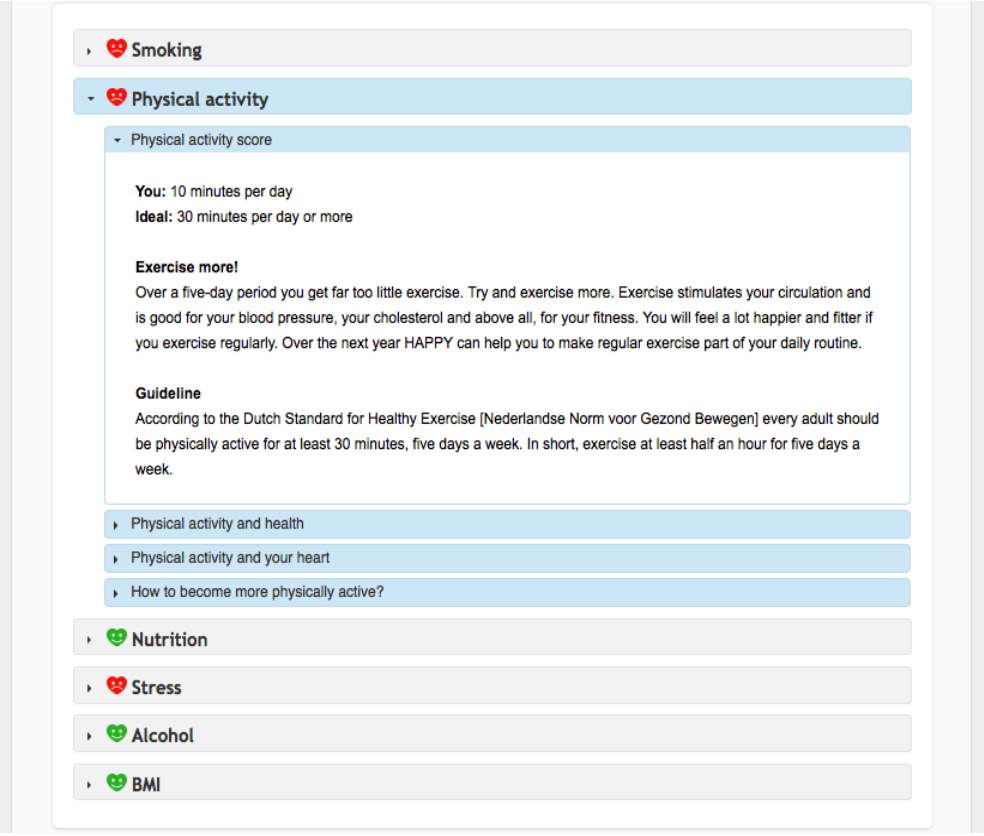


Figure 34. Pop-up boxes on lifestyle page with more information on physical activity

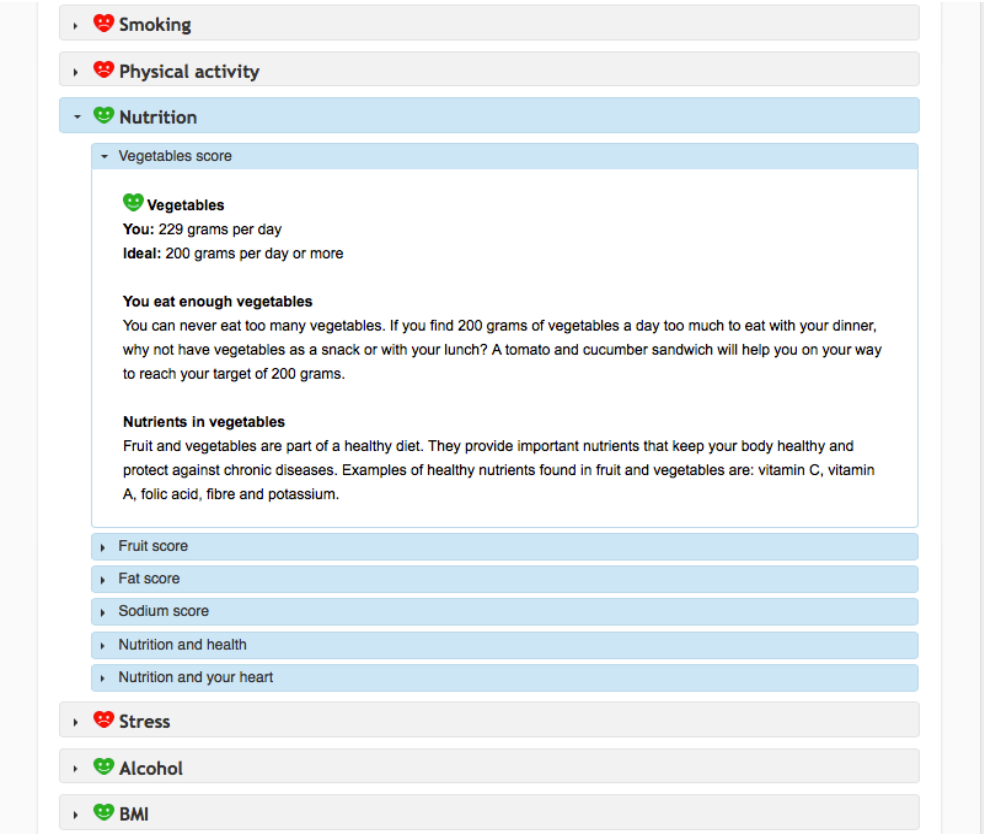


Figure 35. Pop-up boxes on lifestyle page with more information on nutrition

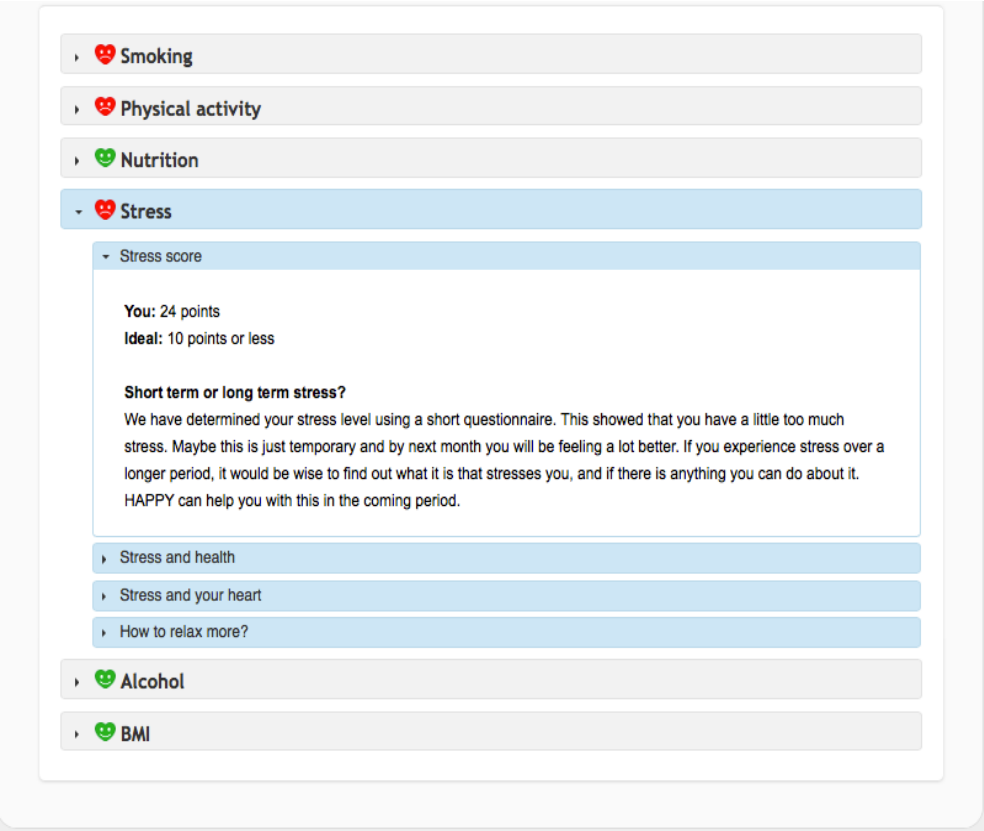


Figure 36. Pop-up boxes on lifestyle page with more information on stress

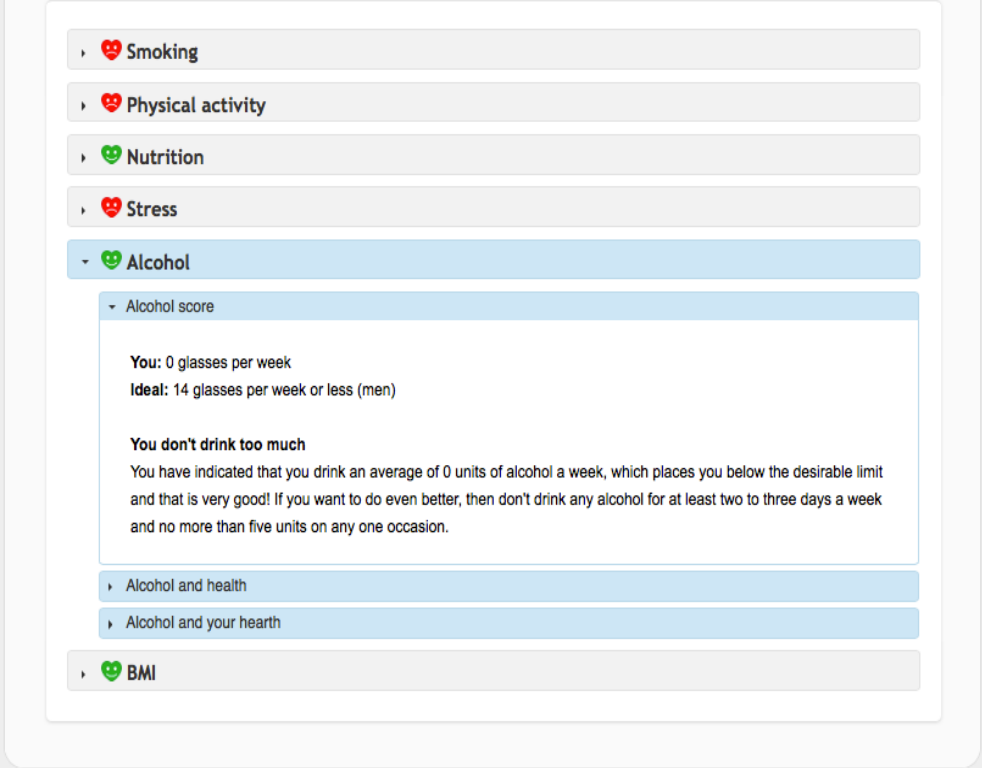


Figure 37. Pop-up boxes on lifestyle page with more information on alcohol

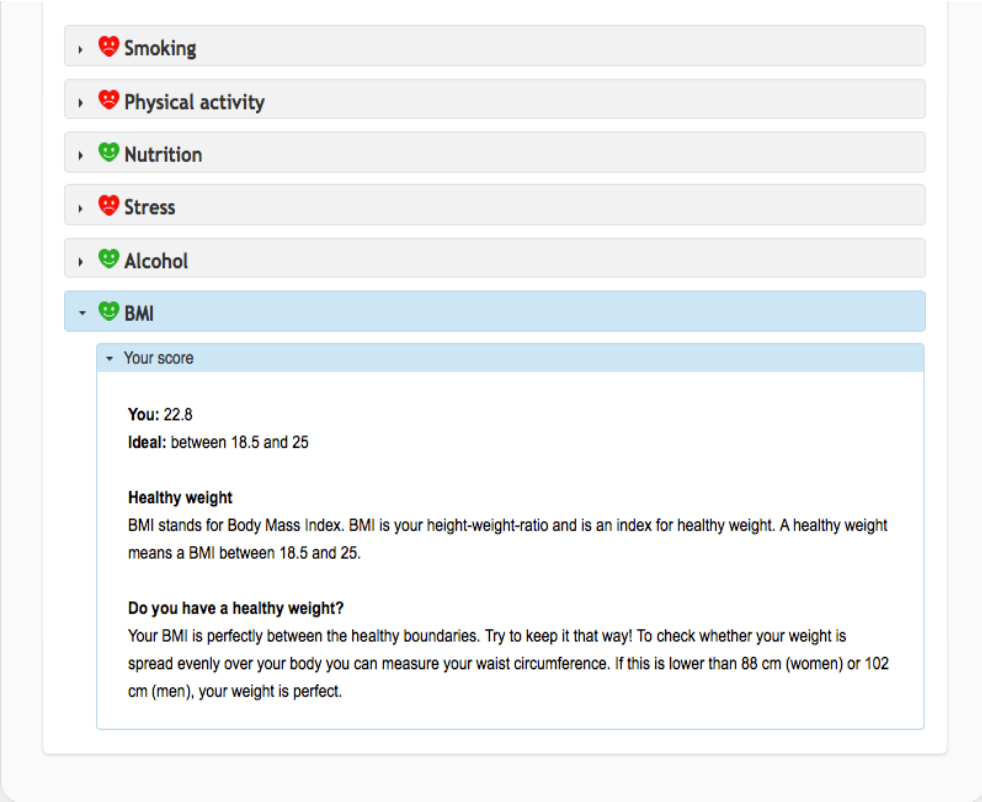


Figure 38. Pop-up boxes on lifestyle page with more information on BMI

Dynamic home page

Over the course of the study the home page for the e-coaching participant got updated with updated lifestyle and heart risk scores. A progress chart was also created with colour-coded bars for each of the visits with changes to the points of improvement based on progress (Figure 39).

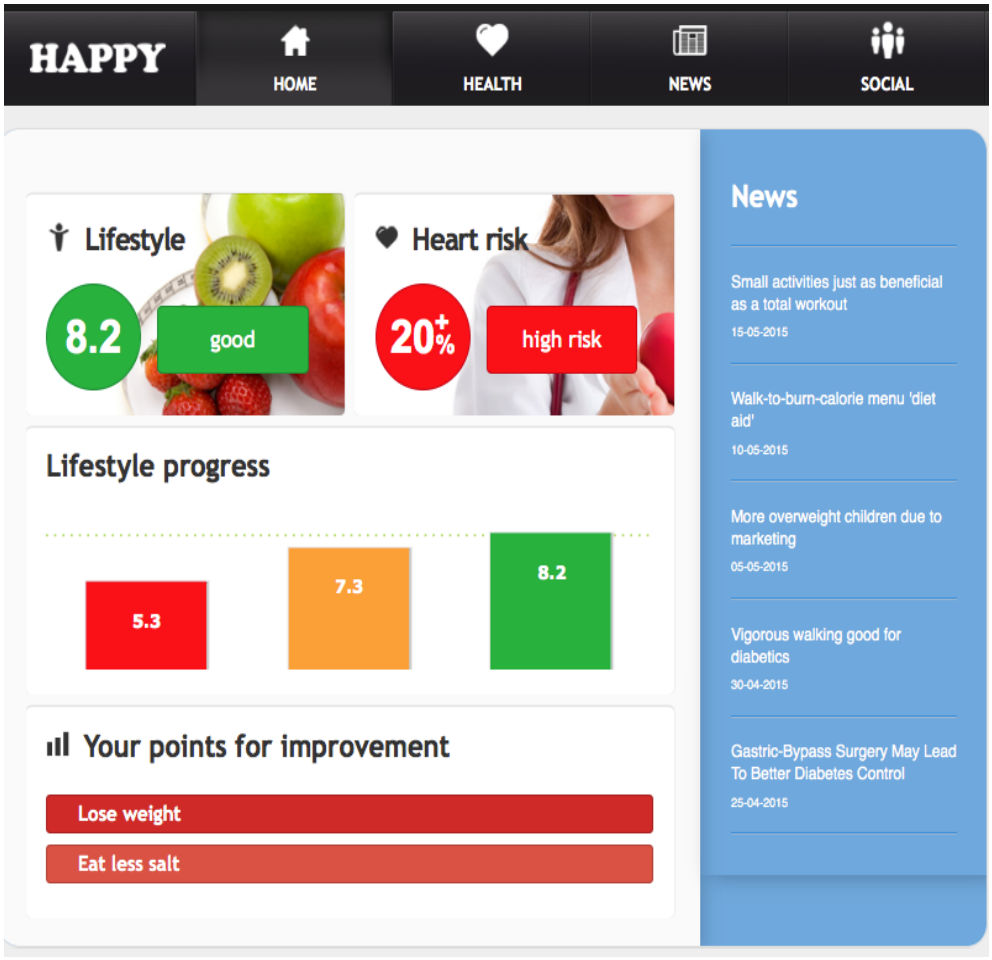


Figure 39. Update of home page during study

Social page

This section of the website allowed participants to share some of their goals and achievements on social media as a means of making others aware and helping to motivate them further. They were also given the opportunity to nominate a 'buddy' (Figure 40). The nominated individual received emails about the personalised goals of the participant during the course of the study. Buddies were advised to

help encourage the participant. The aim of this was to allow further encouragement from people the participant was close to or trusted.

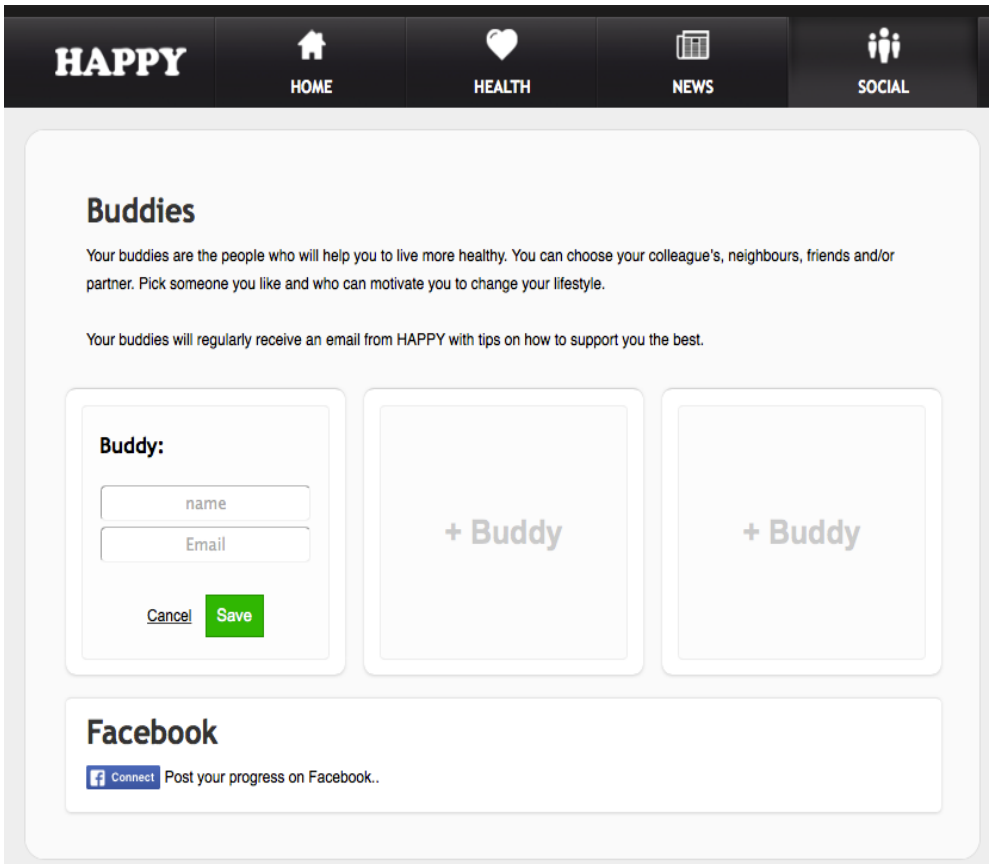


Figure 40. Social page

Researcher data log and administration portal

Overview page

The overview page for the researcher provided study information relating to each participant. It included a summary of all the visits that had already occurred and ones that were booked for future visits. It provided summary details on the front page, whether information about a CMR scan and a summary of the QRISK2, Framingham risk and lifestyle scores from each of the visits for the research team to view (Figure 41). This page provided access to the links for each of the visit data entry sections, automatically generated blood forms with bar codes and scan codes for each participant for the lab to easily scan in. This step was generated to avoid having had to manually input the participant ID number, which may have been

potentially prone to human error. The results of the blood test from each visit and the results of the completed questionnaires were also available from this page.

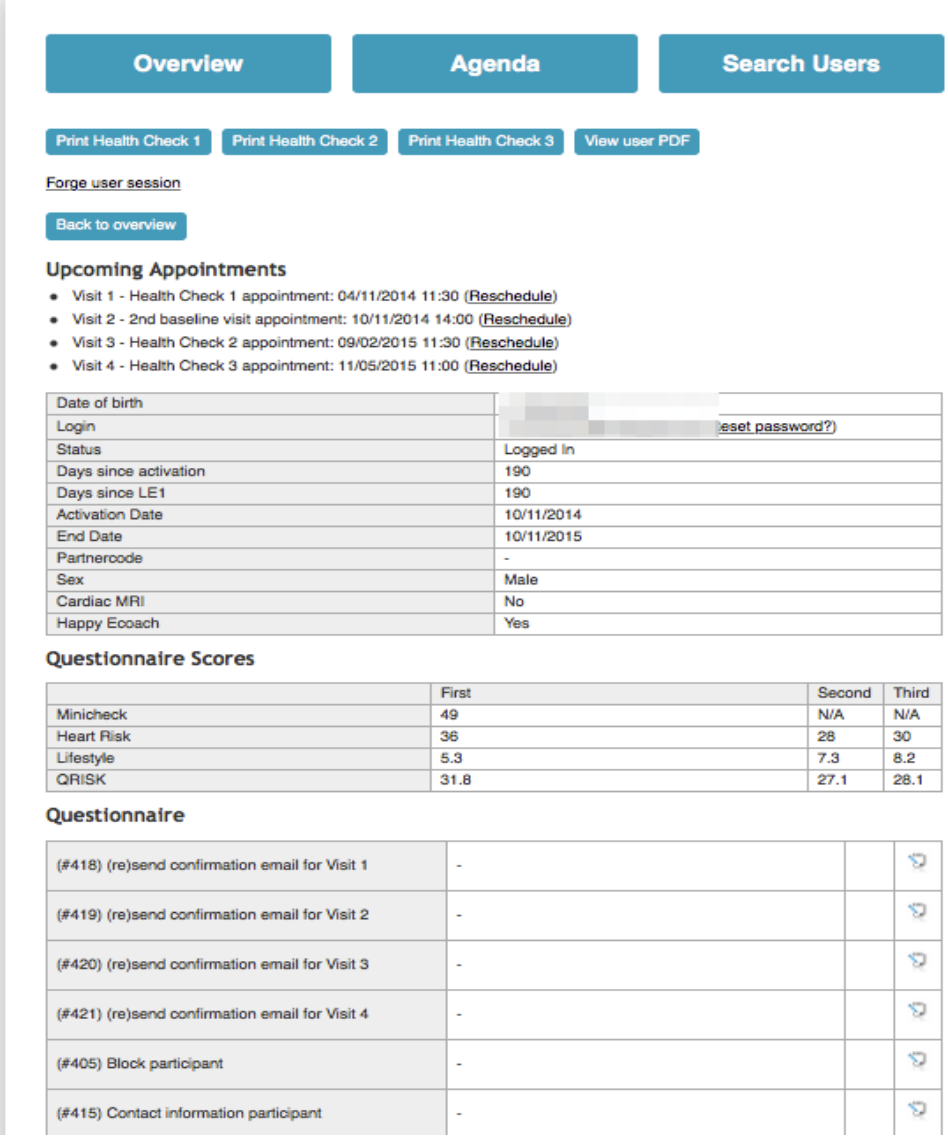


Figure 41. Overview page of each participant for the research team

Researcher page for visit 1 (Screening visit)

During this visit the participant was introduced to the research team member with confirmation that they received the PIS and the consent form. An explanation of the study was given with any queries or concerns raised after information was given and from the PIS or consent form were discussed prior to written consent having been obtained.

Participants then underwent the initial measurements as outlined in the checklist below including BP, height and weight (for BMI), waist circumference, hip circumference and CVD risk factors that form part of the QRISK2 algorithm including history of smoking, diabetes, family history of premature coronary artery disease, atrial fibrillation, rheumatoid arthritis or chronic kidney disease (Figure 42). Confirmation of blood tests having been taken was also required on the form. A note was also made of whether all the consent points had been agreed to for easy future reference and whether those that were potentially eligible for the CMR scan agreed to having a scan as long as there was no safety contraindication. All of this information was written on a form and transferred onto the website for incorporation into both the researcher review pages and also relevant information for personalising the e-coaching group participants' individual profile.

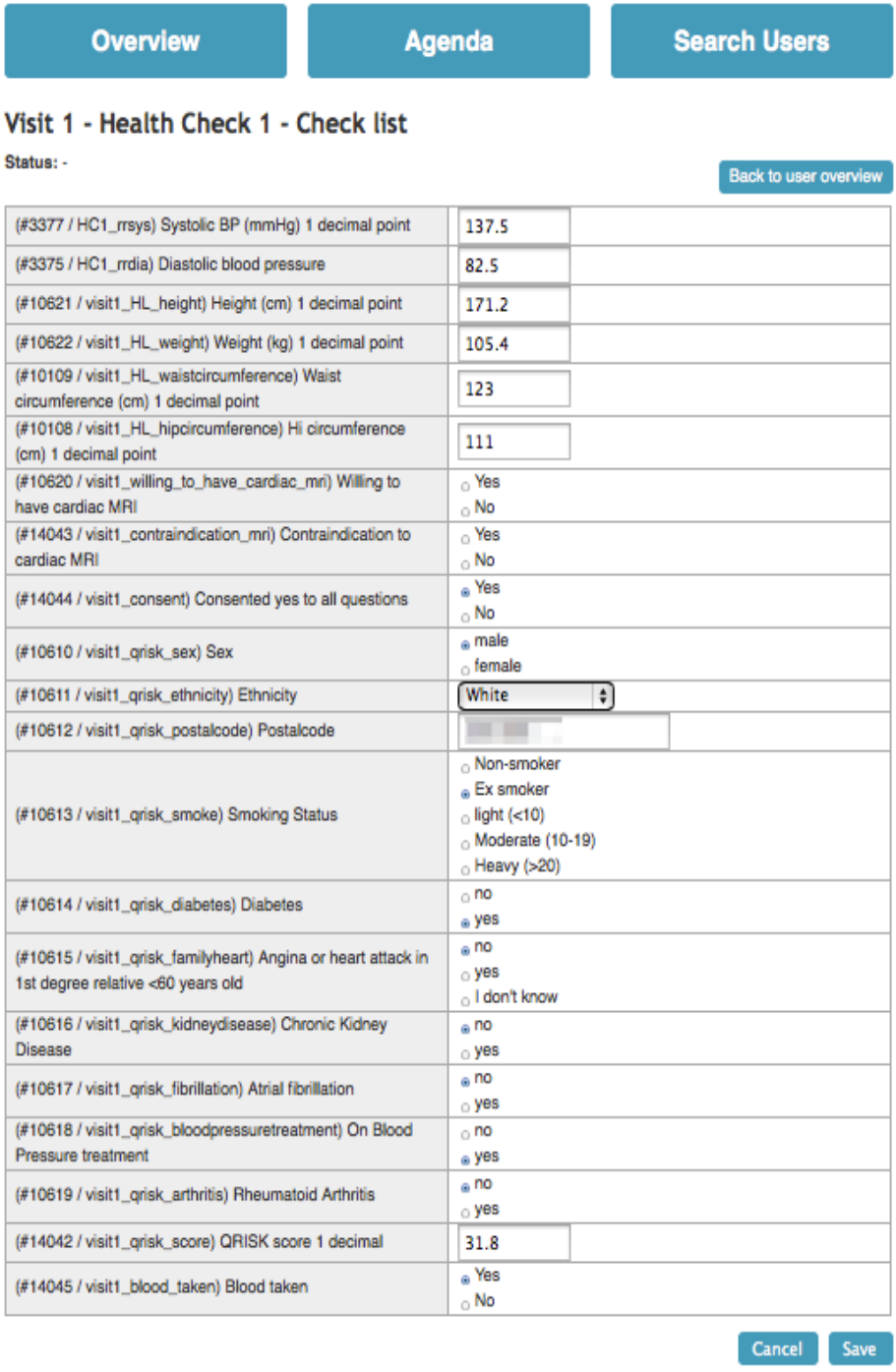


Figure 42. Researcher data input page for visit 1

Blood test results and approval

Blood test results were automatically transferred to the participants' result page from the lab information technology transfer system. This was available to the research team on the following working day after the first visit. A QRISK2 score was calculated and entered on this page. If the participant had a QRISK2 score of

10% or above over the following 10-years then they were deemed eligible to enter the study. This was confirmed and the treatment arm that they had been allocated to based on the randomisation software tool was also entered. It was also confirmed whether they were going to have the CMR scan and the date and time of the next visit. The information was entered onto the lab results/approval page and submitted (Figure 43). The provisional 2nd visit date and time was usually discussed at the first visit and conformed via email. This process then generated an automated email that was sent to the participant. The email informed the participant whether they had been enrolled into the study and provided information on where they should go for the 2nd visit, with a different venue depending on whether a CMR was to be performed or not. CMR patients were given the address for the Barts Health CMR scanning department and all other participants were asked to attend the main research centre. Participants also received a summary of what to expect at the 2nd visit regards tests and were asked to complete the lifestyle, physical activity, quality of life and personality trait questionnaires ideally before the visit. This was made available to them as soon as they logged onto the website after confirmation of enrolment.

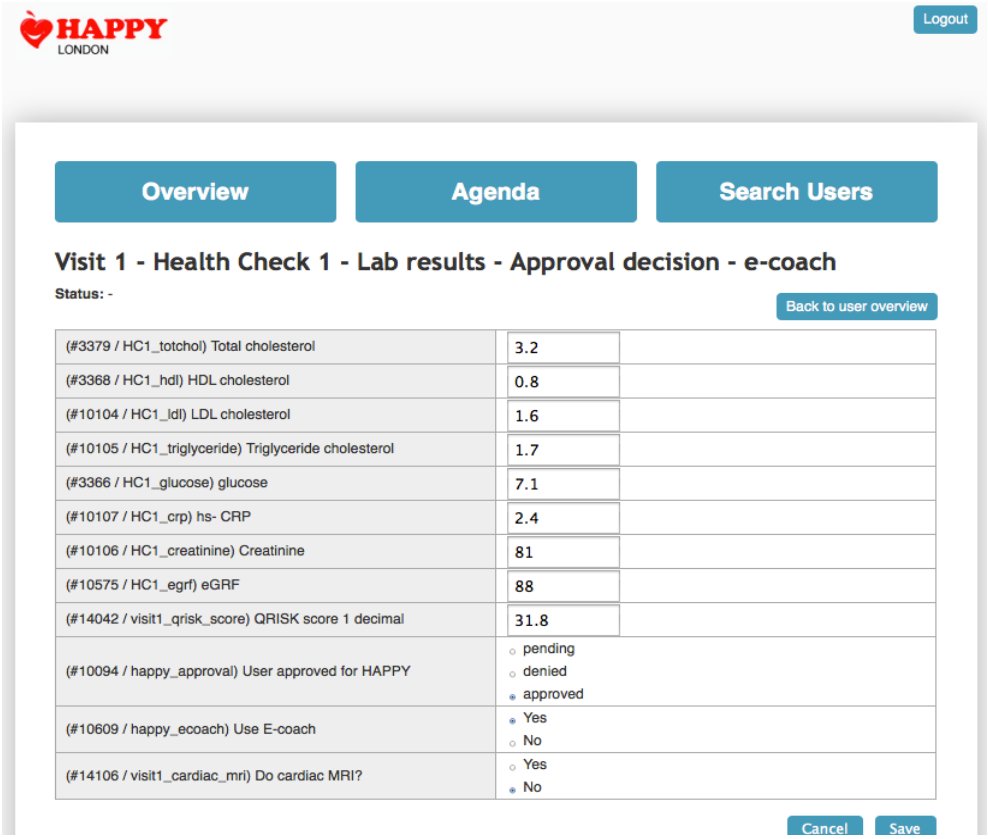


Figure 43. Lab results and approval page

Researcher page for visit 2 (Baseline visit)

Prior to this visit, participants were asked to complete the lifestyle questionnaire. This then formed the main focus of the face-to-face advice that the participant received on trying to improve factors that were identified as being suboptimal. They were also encouraged to complete the quality of life questionnaires and the RPAQ and Personality trait questionnaires around the time of the 2nd visit.

The 2nd visit was usually booked between 2 days from the screening visit and within 2 weeks to allow accurate measurements in a timely fashion. The data from the 2nd HAPPY London study visit, which was the baseline measurement visit for the primary end point of PWV using the Vicorder device was entered. During this visit all participants underwent an ultrasound scan of the carotid arteries looking for carotid plaque in a qualitative manner and also measures of the CIMT bilaterally. This was taken over an area of the common carotid artery, caudal to the bifurcation of the common carotid artery. Vicorder readings of AI and PWV were also entered into the database (Figure 44).

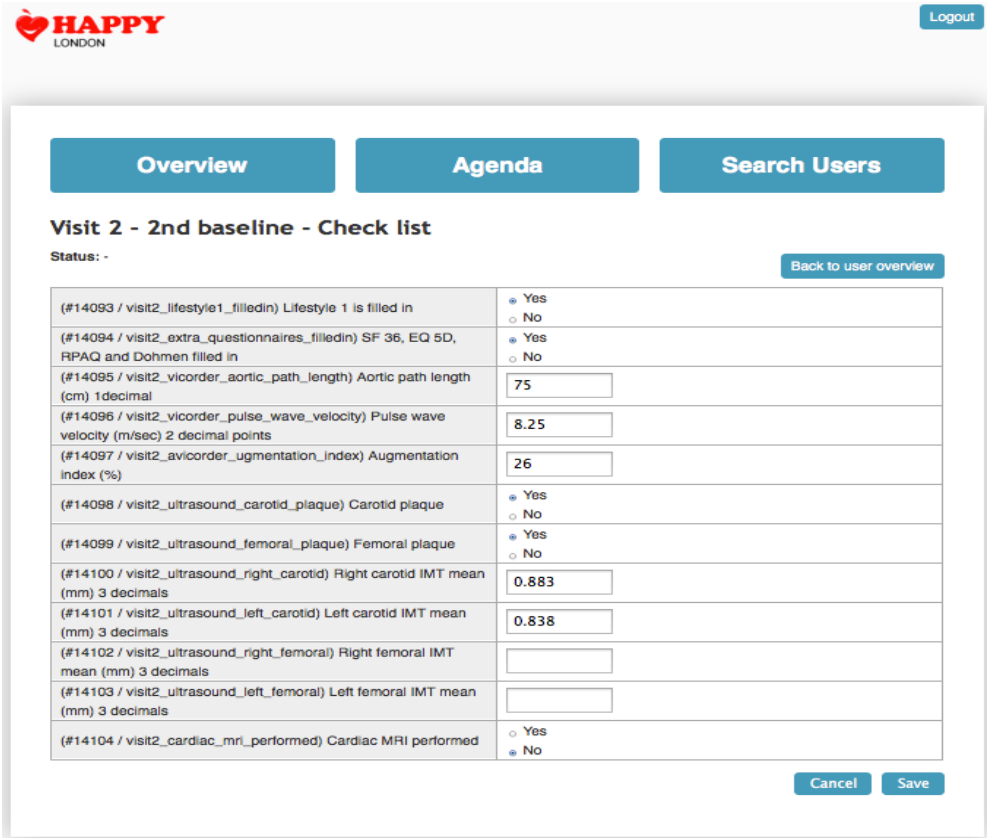
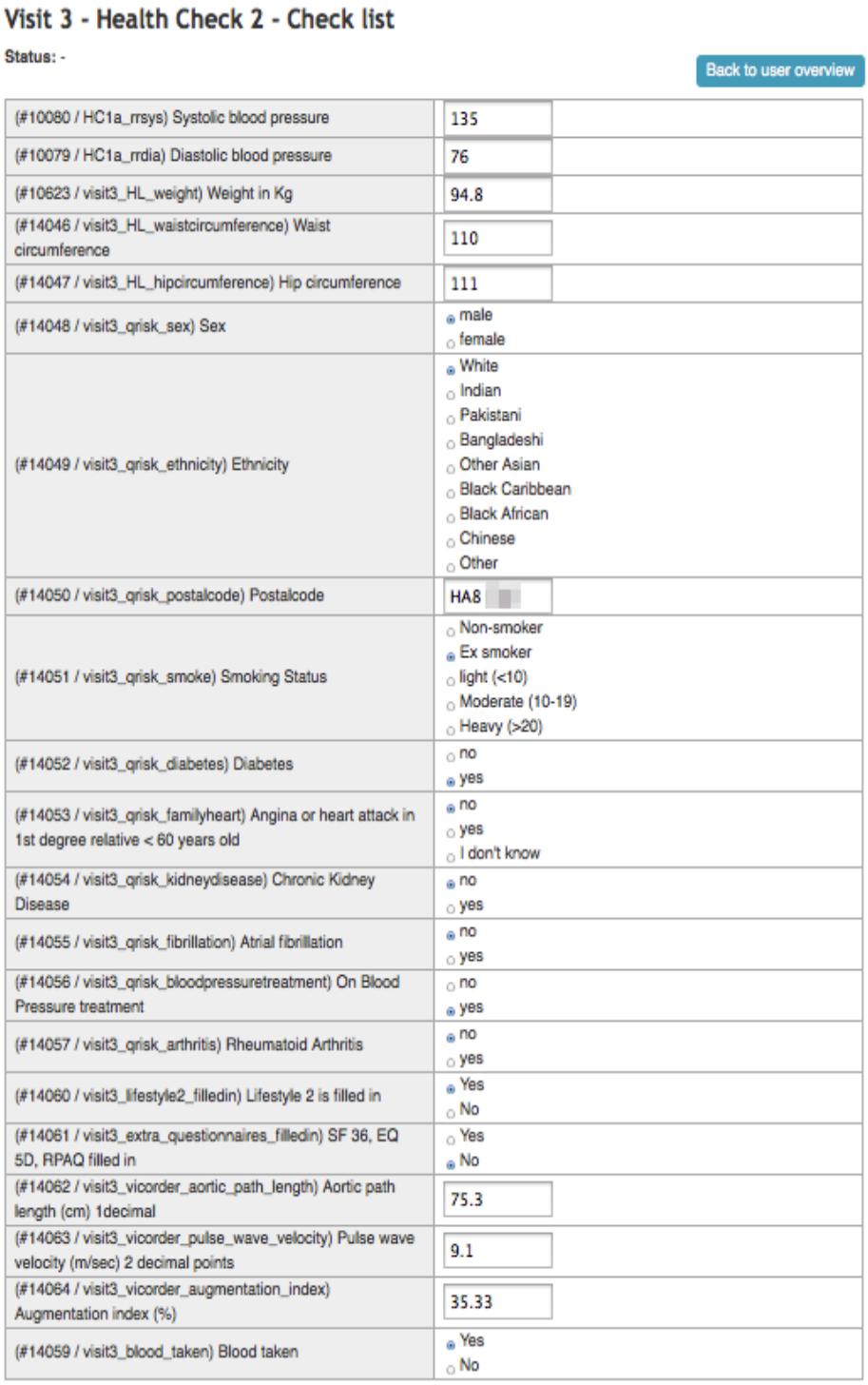


Figure 44. Researcher data input page for visit 2

Researcher page for visit 3

The risk factors and measurements for the 3-month visit were taken at the visit and recorded on the researcher website and were then updated onto the personalised web page of the e-coaching group. Measurement results from the 3-month Vicorder results were also entered (Figure 45).



Visit 3 - Health Check 2 - Check list

Status: -

Back to user overview

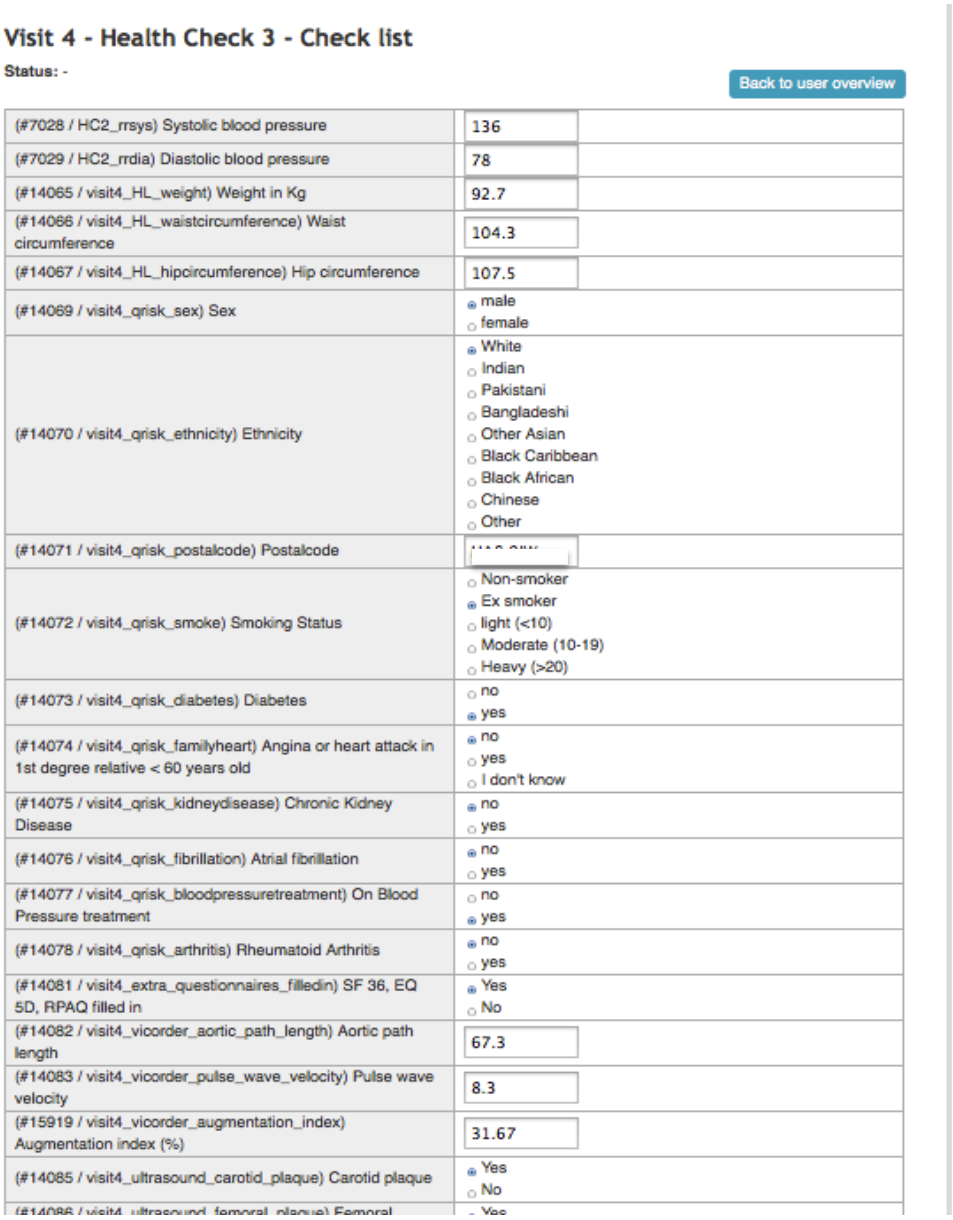
(#10080 / HC1a_rrsys) Systolic blood pressure	135
(#10079 / HC1a_rrdia) Diastolic blood pressure	76
(#10623 / visit3_HL_weight) Weight in Kg	94.8
(#14046 / visit3_HL_waistcircumference) Waist circumference	110
(#14047 / visit3_HL_hipcircumference) Hip circumference	111
(#14048 / visit3_qrisk_sex) Sex	◉ male ○ female
(#14049 / visit3_qrisk_ethnicity) Ethnicity	◉ White ○ Indian ○ Pakistani ○ Bangladeshi ○ Other Asian ○ Black Caribbean ○ Black African ○ Chinese ○ Other
(#14050 / visit3_qrisk_postalcode) Postalcode	HA8
(#14051 / visit3_qrisk_smoke) Smoking Status	○ Non-smoker ◉ Ex smoker ○ light (<10) ○ Moderate (10-19) ○ Heavy (>20)
(#14052 / visit3_qrisk_diabetes) Diabetes	○ no ◉ yes
(#14053 / visit3_qrisk_familyheart) Angina or heart attack in 1st degree relative < 60 years old	◉ no ○ yes ○ I don't know
(#14054 / visit3_qrisk_kidneydisease) Chronic Kidney Disease	◉ no ○ yes
(#14055 / visit3_qrisk_fibrillation) Atrial fibrillation	◉ no ○ yes
(#14056 / visit3_qrisk_bloodpressuretreatment) On Blood Pressure treatment	○ no ◉ yes
(#14057 / visit3_qrisk_arthritis) Rheumatoid Arthritis	◉ no ○ yes
(#14060 / visit3_lifestyle2_filledin) Lifestyle 2 is filled in	◉ Yes ○ No
(#14061 / visit3_extra_questionnaires_filledin) SF 36, EQ 5D, RPAQ filled in	○ Yes ◉ No
(#14062 / visit3_vicorder_aortic_path_length) Aortic path length (cm) 1decimal	75.3
(#14063 / visit3_vicorder_pulse_wave_velocity) Pulse wave velocity (m/sec) 2 decimal points	9.1
(#14064 / visit3_vicorder_augmentation_index) Augmentation index (%)	35.33
(#14059 / visit3_blood_taken) Blood taken	◉ Yes ○ No

Figure 45. Researcher data input page for visit 3

Researcher data input page for visit 4

The data input page provided the opportunity to note down the measurements from the 6-month final visit to obtain the risk factors required to acquire a QRISK2 score, Vicorder readings and the ultrasound measures of CIMT and presence of atheromatous plaque (Figure 46). It was also recorded if the participant had a CMR scan at the final visit.

Any change in risk factors was also recorded. Participants were also asked about medication change, any unscheduled GP visits as a result of taking part in the study and any hospital admissions that may have taken place during the study period, although this information was not entered onto the website for simplicity. It was however documented in their records and a tally was kept of how many had any changes or initiation of CVD medication, with particular emphasis on BP and cholesterol lowering medication.



Visit 4 - Health Check 3 - Check list

Status: -

Back to user overview

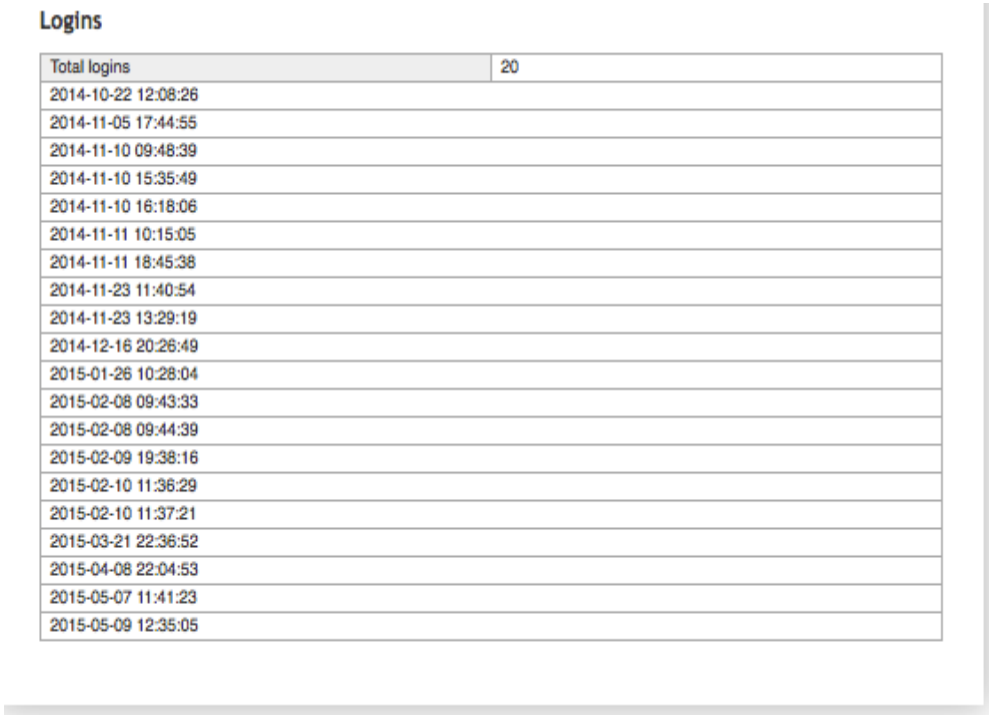
(#7028 / HC2_rrsys) Systolic blood pressure	136
(#7029 / HC2_rrdia) Diastolic blood pressure	78
(#14065 / visit4_HL_weight) Weight in Kg	92.7
(#14066 / visit4_HL_waistcircumference) Waist circumference	104.3
(#14067 / visit4_HL_hipcircumference) Hip circumference	107.5
(#14069 / visit4_qrisk_sex) Sex	male female
(#14070 / visit4_qrisk_ethnicity) Ethnicity	White Indian Pakistani Bangladeshi Other Asian Black Caribbean Black African Chinese Other
(#14071 / visit4_qrisk_postalcode) Postalcode	
(#14072 / visit4_qrisk_smoke) Smoking Status	Non-smoker Ex smoker light (<10) Moderate (10-19) Heavy (>20)
(#14073 / visit4_qrisk_diabetes) Diabetes	no yes
(#14074 / visit4_qrisk_familyheart) Angina or heart attack in 1st degree relative < 60 years old	no yes I don't know
(#14075 / visit4_qrisk_kidneydisease) Chronic Kidney Disease	no yes
(#14076 / visit4_qrisk_fibrillation) Atrial fibrillation	no yes
(#14077 / visit4_qrisk_bloodpressuretreatment) On Blood Pressure treatment	no yes
(#14078 / visit4_qrisk_arthritis) Rheumatoid Arthritis	no yes
(#14081 / visit4_extra_questionnaires_filledin) SF 36, EQ 5D, RPAQ filled in	Yes No
(#14082 / visit4_vicorder_aortic_path_length) Aortic path length	67.3
(#14083 / visit4_vicorder_pulse_wave_velocity) Pulse wave velocity	8.3
(#15919 / visit4_vicorder_augmentation_index) Augmentation index (%)	31.67
(#14085 / visit4_ultrasound_carotid_plaque) Carotid plaque	Yes No
(#14086 / visit4_ultrasound_femoral_plaque) Femoral	Yes

Figure 46. Researcher data input page for visit 4

Record of participant logins

Details of the number of times that each participant logged into the account were also available (Figure 47). All participants would be required to log in to complete the questionnaires regardless of which treatment arm they belonged to. This factor potentially provided the average additional number of times that e-coaching group may have accessed the website to review their information. Participants were not instructed on the minimum or maximum number of times that they should review their e-coaching web page. They were advised to visit the page as often as they wished. The e-coaching group also received tailored emails in addition to access to

their lifestyle and risk factor results. The number of emails were personalised based on the number of potentially suboptimal factors. Participants with more sub optimal factors would receive more frequent emails covering the various risk factors that needed addressing. General health emails were also sent based on contemporary research findings on lifestyle and CVD risk reduction. Participants had the option of turning these functions off.



Logins

Total logins	20
2014-10-22 12:08:26	
2014-11-05 17:44:55	
2014-11-10 09:48:39	
2014-11-10 15:35:49	
2014-11-10 16:18:06	
2014-11-11 10:15:05	
2014-11-11 18:45:38	
2014-11-23 11:40:54	
2014-11-23 13:29:19	
2014-12-16 20:26:49	
2015-01-26 10:28:04	
2015-02-08 09:43:33	
2015-02-08 09:44:39	
2015-02-09 19:38:16	
2015-02-10 11:36:29	
2015-02-10 11:37:21	
2015-03-21 22:36:52	
2015-04-08 22:04:53	
2015-05-07 11:41:23	
2015-05-09 12:35:05	

Figure 47. Record of number of times participant logged onto website

Chapter 5- Cardiovascular Risk Assessment: A Systematic Review of Guidelines

Preamble

In this chapter I performed a systematic review of the current primary prevention guidelines on cardiovascular risk assessment to try and identify how e-coaching could be incorporated into the system. I considered factors such as risk assessment and the recommendations that the guideline author's make regards its use in identifying target populations or for making decisions on management and whether there is a consensus in these recommendations. In the HAPPY London study I included individuals who had elevated cardiovascular risk based on the UK validated QRISK2 algorithm.

Abstract

Background: Many guidelines exist for screening and risk assessment for the primary prevention of CVD in apparently healthy persons.
Purpose: To systematically review current primary prevention guidelines on adult cardiovascular risk assessment and highlight the similarities and differences to aid clinician decision-making.

Data sources: Publications in MEDLINE and CINAHL between 3 May 2009 and 30 June 2016 were identified. On 30 June 2016, the Guidelines International Network International Guideline Library, National Guideline Clearinghouse, National Library for Health Guidelines Finder, Canadian Medical Association Clinical Practice Guidelines Infobase, and Web sites of organisations responsible for guideline development were searched.

Study selection: 2 reviewers screened titles and abstracts to identify guidelines from Western countries containing recommendations for cardiovascular risk assessment for healthy adults.

Data extraction: 2 reviewers independently assessed rigor of guideline development using the Appraisal of Guidelines for Research and Evaluation II instrument, and 1 extracted the recommendations.

Data synthesis: Of the 21 guidelines, 17 showed considerable rigor of development. These recommendations address assessment of total cardiovascular risk (5 guidelines), dysglycaemia (7 guidelines), dyslipidaemia (2 guidelines), and hypertension (3 guidelines). All but 1 recommendation advocated for screening, and most included prediction models integrating several relatively simple risk factors for either deciding on further screening or to guide subsequent management. No consensus on the strategy for screening, recommended target population, screening tests, or treatment thresholds exists.

Limitation: Only guidelines developed by Western national or international medical organizations were included.

Conclusion: Considerable discrepancies in cardiovascular screening guidelines still exist, with no consensus on optimum screening strategies or treatment threshold.

Background

Many national and international bodies highlight primary prevention of CVD through risk factor reduction as a potential solution to reduce future burden [2]. The optimal target group and intervention that maximises benefit, however, remains unclear. Cardiovascular screening during health checks is now widely implemented in many Western countries to systematically detect high-risk persons who may require aggressive risk reduction through pharmacotherapy or lifestyle interventions[89]. Guidelines advocate use of screening with the aim of improving the health of an already healthy population and reducing risk factors for future CVD. The Institute of Medicine defines clinical practice guidelines as "systematically developed statements to assist practitioners and patient decisions about the appropriate health care for specific clinical circumstances" [180]. However, to date, an internationally agreed-on guideline for cardiovascular health checks does not exist.

Primary care physicians maintain a central role in the prevention of CVD but still find implementation of prevention strategies challenging, and management of persons with increased CVD risk remains suboptimal [181]. Time constraints, lack of perceived usefulness, inadequate knowledge, and inconsistency in published recommendations have been cited as common reasons for not using CVD prevention guidelines or global CVD risk assessment tools [182]. Concerns exist about poor uptake of the NHS Health Check program; only about 50% of those invited—much lower than the 75% government target—attended [183]. In addition, a Cochrane review and subsequent Danish randomised, controlled trial raised doubts about the morbidity and mortality benefits from such programs [184,185].

Ferket and colleagues performed a systematic review in 2010, which identified differences among guidelines that would lead to variations in allocation of resources for prevention among Western health care systems [89]. Since then, the reviewed guidelines were revised and replaced, and new evidence has also become available on statin and BP–lowering therapy for low-risk persons [29,186]. This systematic review revisits the CVD risk assessment guidelines and the selection of appropriate screening interventions based on currently available evidence.

Methods

Data source and searches

I conducted an updated systematic review, using the previous search strategy used by our collaborators from the Erasmus Medical College [89], of guidelines containing recommendations for CVD risk assessment in the apparently healthy adult population not already receiving treatment for high-risk cardiovascular conditions, such as diabetes, hypertension, and hypercholesterolemia. I searched for published guidelines using MEDLINE and CINAHL between 3 May 2009 and 30 June 2016 (See Appendix). The 4 following guideline-specific databases supplemented our search: National Guideline Clearinghouse (USA), National Library for Health Guidelines Finder (UK), Canadian Medical Association Clinical Practice Guidelines InfoBase, and Guidelines International Network International Guideline Library. I also searched many Web sites of guideline development organisations, including those affiliated with all of the guidelines included in our previous publication, to find relevant additional or updated guidelines (Table 5). Our search was restricted to national guidelines from the USA, Canada, UK, Australia, and New Zealand and international guidelines written in English.

Table 5. Web site searches of guideline development organisations, including web sites affiliated with all the guidelines included in our previous publication

Organisation Responsible for Guideline Development	Country	Web Site Searched
American Academy of Family Physicians	United States	www.aafp.org/online/en/home.html
American Association of Clinical Endocrinologists	United States	www.aace.com
American College of Cardiology	United States	www.acc.org
American College of Physicians	United States	www.acponline.org/
American College for Preventive Medicine	United States	www.acpm.org
American Diabetes Association	United States	www.diabetes.org/
American Geriatrics Society	United States	www.americangeriatrics.org/
American Heart Association	United States	www.americanheart.org/
American Medical Association	United States	www.ama-assn.org/
American Stroke Association	United States	www.strokeassociation.org/
Australian Diabetes Society	Australia	www.diabetessociety.com.au/
Australian Medical Association	Australia	www.ama.com.au/web.nsf/

British Cardiac Society	United Kingdom	www.bcs.com/pages/default.asp
British Hypertension Society	United Kingdom	www.bhsoc.org/default.stm
Canadian Diabetes Association	Canada	http://guidelines.diabetes.ca
Canadian Hypertension Society	Canada	www.hypertension.ca
Canadian Task Force on Preventive Health Care	Canada	http://canadiantaskforce.ca
Cardiac Society of Australia and New Zealand	Australia	www.csanz.edu.au
Centres for Disease Control and Prevention/American Heart Association	United States	www.cdc.gov
Department of Health	United Kingdom	www.dh.gov.uk/en/index.htm
European Society of Cardiology	Europe	www.escardio.org/
International Diabetes Federation	International	www.idf.org/
International Society of Hypertension	International	www.ish-world.com/
National Health and Medical Research Council	Australia	www.nhmrc.gov.au/index.htm
National Heart Foundation	Australia	www.heartfoundation.org.au/index.htm
National Heart Lung and Blood Institute	United States	www.nhlbi.nih.gov/guidelines/index.htm
National Institute for Health and Care Excellence	United Kingdom	www.nice.org.uk/
New Zealand Guidelines Group	New Zealand	www.nzgg.org.nz/index.cfm?
Royal College of General Practitioners	United Kingdom	www.rcgp.org.uk/default.aspx
Scottish Intercollegiate Guidelines Network	United Kingdom	www.sign.ac.uk
U.S. Preventive Services Task Force	United States	www.ahrq.gov/clinic/uspstfix.htm
World Heart Federation	International	www.world-heart-federation.org
World Health Organisation	International	www.who.int/en
World Hypertension League	International	www.worldhypertensionleague.org/Pages/Home.aspx
International Diabetes Federation European Region	International	http://diabetespreventionforum.org/index.php/projects/6-image-project

Study selection

References that met the Institute of Medicine's definition of a guideline were included. Guidelines were excluded if they did not contain recommendations involving the healthy adult population, were entirely focused on early detection of CVD, were not produced on behalf of a professional organisation, or were not applicable to Western countries. In addition, only guidelines produced or updated as of May 2009 were eligible for inclusion to avoid overlap with our previous systematic review and ensure that only current guidelines were included.

Data extraction and quality assessment

Titles and abstracts were assessed by 2 independent reviewers (Vinicius Bicalho and I). Articles were excluded only if both reviewers agreed that they were ineligible. Discrepancies were resolved by consensus after discussion. Both reviewers performed the final selection for full data extraction.

I used the latest 23-item Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument to determine the rigor of development for each guideline [187]. This domain considers reporting of methods to search for evidence; criteria for selection of evidence; strengths and limitations of the body of evidence; methods for formulating the recommendations; health benefits, side effects, and risks; explicit link between recommendations and evidence; procedures for external expert peer review; and the updating process. Each item is rated on a 7-point Likert scale. Conforming to the instructions of the AGREE II tool, 2 reviewers (Claudia van Waardhuizen and I) independently rated the items. Both reviewers assessed background information on the guideline development process from developers' Web sites. Average rigor scores were obtained by expressing the sum of the individual scores as a percentage of the maximum possible score. Reproducibility of the 2 reviewers' scores was good, with an interclass correlation of 0.75 (comparing the agreement of the total rigor of development score obtained by the two reviewers (Claudia van Waardhuizen and I, for all the 21 guidelines assessed with the AGREEII tool; where a score of 1 would mean perfect agreement between the scores). I ranked the guidelines according to their scores. Editorial independence from the funding body, external funding, and disclosure of relationships with the industry by individual guideline group members were also assessed.

Data synthesis and analysis

I extracted all of the relevant recommendations from the guidelines that had an AGREE II score greater than 50%. General lifestyle advice was not included. A recommendation matrix was produced and grouped by the conditions being detected by screening. Each matrix was divided into methods, target group and

delivery of screening, recommended screening test, and follow-up thresholds. Consistent with our previous format, the strength of recommendation was classified as "for", "consider," "not for not against," "insufficient evidence", and "against." If feasible, cardiovascular risk factors were classified into major, underlying, and emerging risk factors according to the World Heart and Stroke Forum scientific statement [188].

Role of the funding source

This work was primarily funded as part of a large project grant from Barts Charity. It also forms part of the research areas contributing to the translational research portfolio of the Barts Cardiovascular Biomedical Research Unit, which is supported and funded by the NIHR (Professor Steffen Petersen and I). The Barts Charity and the NIHR had no role in the design of the study; the collection, analysis, and interpretation of the data; or the decision to approve publication of the finished manuscript.

Results

My search retrieved 3553 titles, of which 180 were identified as potentially eligible. On the basis of the abstracts, I excluded 133 articles. After I reviewed the full reports, 26 more were excluded. Such guidelines as the U.S. Preventative Service Task Force (USPSTF) recommendations on aspirin use were excluded because they did not include recommendations on screening healthy adults [189]. I included 21 guidelines on cardiovascular risk assessment (Figure 48). Table 6 summarises the selected guidelines, along with rigor scores and conflicts of interest.

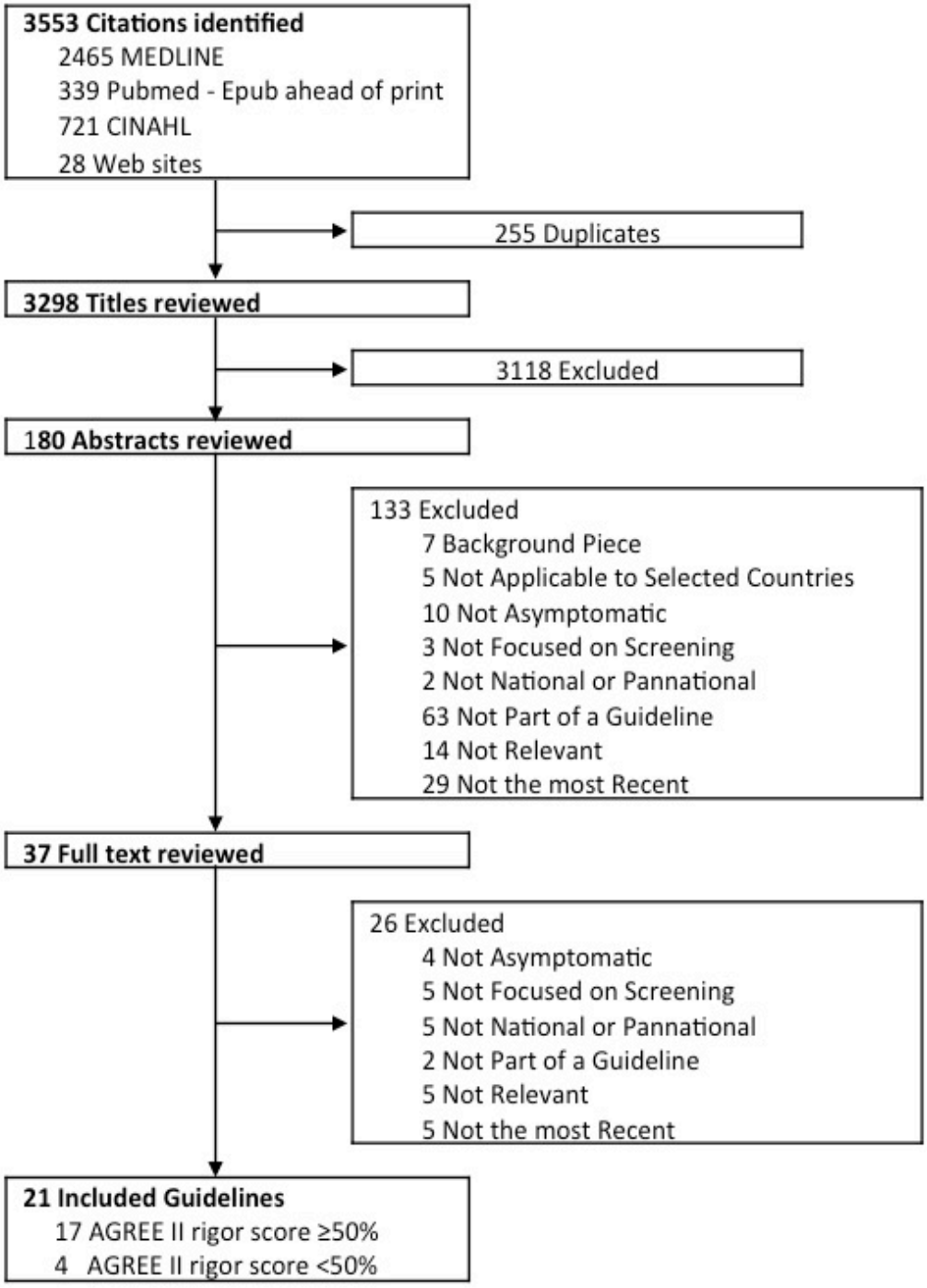


Figure 48. Guideline selection process from searched articles

Table 6. Characteristics of 21 Guidelines

Study, Year (Reference)	Organisation Responsible for Guideline Development	Country Applied	AGREE II Rigor Score, %	Conflicts of Interest
Total cardiovascular risk				
National Clinical Guideline Centre, 2014 [31]	National Institute for Health and Care Excellence	United Kingdom	86	EI, SCI*†
Piepoli et al, 2016 [19]	European Society of Cardiology	Europe	86	SCI*
National Vascular Disease Prevention Alliance, 2012 [190]	National Vascular Disease Prevention Alliance	Australia	85	EI, SCI†
Stone et al, 2014 [69] Goff et al, 2014 [34] Eckel et al, 2014 [20]	American College of Cardiology	United States	83	SCI*†
Mosca et al, 2011 [191]	Centre for Disease Control and Prevention	United States	65	EI, SCI*†
JBS3 Board, 2014 [17]	British Cardiovascular Society	United Kingdom	45	SCI*
New Zealand Guidelines Group, 2012 [192]	New Zealand Guidelines Group	New Zealand	20	EI, SCI‡
Dyslipidaemia				
Reiner et al, 2011 [193]	European Society of Cardiology	Europe	72	SCI*
Jellinger et al, 2012 [194]	American Association of Clinical Endocrinologists	United States	64	SCI*
Anderson et al, 2013 [195]	Canadian Cardiovascular Society	Canada	42	EI, SCI*
Dysglycaemia				
Diabetes Australia, 2010 [196]	Australian Diabetes Society	Australia	87	SCI‡
Booth et al, 2013 [197]	Canadian Diabetes Association	Canada	83	EI, FIP, SCI*†
American Diabetes Association, 2016 [198]	American Diabetes Association	United States	68	SCI*
Siu, 2015 [199]	U.S. Preventive Services Task Force	United States	76	EI, SCI
National Institute for Health and Care Excellence, 2012 [200]	National Institute for Health and Care Excellence	United Kingdom	73	–
Pottie et al, 2012 [201]	Canadian Task Force on Preventive Health Care	Canada	68	EI, SCI*
Rydén et al, 2013 [202]	European Society of Cardiology	Europe	66	SCI*
International Diabetes Federation Guideline Development Group, 2014 [203]	International Diabetes Federation	International	47	FIP, SCI§
Hypertension				
Dasgupta et al, 2014	Hypertension Canada	Canada	90	EI, SCI*†

[204] Daskalopoulou et al, 2015 [205]				
Siu, 2015 [27]	U.S. Preventive Services Task Force	United States	79	EI, SCI
Lindsay et al, 2013 [206]	Canadian Task Force on Preventive Health Care	Canada	78	SCI

AGREE II = Appraisal of Guidelines for Research and Evaluation; EI = editorial with independence declared; FIP = funding by industrial partner reported; SCI = statement about conflicts of interest of group members present.

* Relationship with industry was reported by any group member.
† A group member was reported recused when a relevant area was under discussion.
‡ Conflicts of interest available only on request.
§ Conflicts of interest reported only to the group.

Seventeen of the 21 guidelines had a rigor score of 50% or greater. Guidelines were categorised according to the main purpose of the screening. These included 5 guidelines for total cardiovascular screening (Table 7), 7 guidelines for dysglycaemia screening (Table 8), 2 guidelines for dyslipidaemia screening (Table 9), and 3 guidelines for hypertension screening (Table 10).

Table 7. Recommendations for screening for total CVD risk in 5 guidelines

Variable	European Society of Cardiology	National Institute for Health and Care Excellence	National Vascular Disease Prevention Alliance	American College of Cardiology/American Heart Association	Centres for Disease Control and Prevention/American Heart Association
Country	Europe	United Kingdom	Australia	United States	United States
Year	2016	2014	2012	2013	2011
Appraisal of Guidelines for Research and Evaluation II rigor score, %	86	86	85	83	65
Method to evaluate evidence	Systematic review	Systematic review	Systematic review	Systematic review	Systematic review
Method to formulate recommendations	Formal consensus	Formal consensus	Formal consensus	Formal consensus	Formal consensus and voting
Consideration of costs	Review of CEAs	Systematic review of published literature/performed CEA	Review of CEAs	Not performed	Review of CEAs
Target group	Men aged >40 y and women aged >50 y or who are postmenopausal	Persons aged 40–74 y (National Health Service Health Check)	All adults aged >45 y or Aboriginal and Torres Strait Islanders aged >35 y	Persons aged ≥21 y	Women aged ≥20 y
Strategy	Opportunistic screening/case finding	Opportunistic screening/case finding/record-based	Opportunistic screening/case finding	Opportunistic screening/case finding	NR
Strength of recommendation	For	For	For	For	Not for and not against
Prediction model	Systematic Coronary Risk Evaluation; general atherosclerotic CVD mortality at 10 y	QRISK2; CHD/stroke/TIA events at 10 y	FRS; CHD/stroke events at 5 y	Pooled cohort equations; CHD/stroke events at 10 y if aged 40–79 y or lifetime (30-y) risk for persons aged 20–59 y with 10-y risk ≤7.5%	FRS/Reynolds Risk Score; CHD/stroke at 10 y

Risk factors					
Age	*	*	*	*	*
Sex	*	*	*	*	*
BP	*	*	*	*	*
Total cholesterol level	*	*	*	*	*
LDL cholesterol level	†	†	†	–	–
HDL cholesterol level	*	*	*	*	*
Total cholesterol–HDL cholesterol ratio	*	*	*	*	–
Smoking	*	*	*	*	*
Glucose levels	–	†	†	–	–
Underlying risk factors					
Overweight/obesity	†	*	†	–	*
Physical inactivity	†	–	†	–	*
Atherogenic diet	–	–	–	–	–
Socioeconomic factors	†	*	†	–	–
Family history of premature CVD	†	*	†	‡	*
Genetic/racial factors	†	*	†	*	*
Diabetes	†	*	*	*	*
Antihypertensives	†	*	–	*	–
Emerging risk factors					
Triglyceride levels	†	†	†	–	–
Renal function	†	*	†	–	*
Heart rate	†	–	–	–	–
Apolipoprotein lipoprotein levels	§	–	–	–	–
Glucose therapy for insulin resistance	–	–	–	–	–
Prothrombotic markers	§	–	–	–	–
C-reactive protein level	§	–	–	‡	–
Subclinical atherosclerosis	§ (Ankle–brachial index; coronary artery calcium score; and carotid ultrasonography for plaque)	–	* (Left ventricular hypertrophy)	‡ (Ankle–brachial index and coronary artery calcium score)	–
Thresholds					
Aspirin	Not recommended in	NA	Not recommended in	NA	May be useful in

	primary prevention		primary prevention		women aged ≥65 y depending on benefit vs. risk assessment; reasonable in DM
Statins	10-y CVD mortality ≥10% and LDL cholesterol level ≥1.813 mmol/L (70 mg/dL); 10-y risk of 5%–10% and LDL cholesterol level ≥2.590 mmol/L (100 mg/dL); consider if 10-y risk <5% and LDL cholesterol level >2.979 mmol/L (115 mg/dL); type 2 DM or type 1 DM and age >40 y	10-y CHD/stroke/TIA risk ≥10%; type 2 DM and 10-y CVD risk ≥10%‖; type 1 DM; CKD with estimated glomerular filtration rate <60 mL/min/1.73 m^2	5-y CHD/stroke risk ≥15%; persistent BP ≥160/100 mm Hg; total cholesterol level >7.5 mmol/L (290 mg/dL); 5-y CHD/stroke risk of 10%–15% and family history of premature CVD	40–75 y with 10-y CHD/stroke risk ≥7.5% and LDL cholesterol level of 1.813–4.895 mmol/L (70–189 mg/dL); aged 40–75 y with DM and LDL cholesterol level of 1.813–4.895 mmol/L (70–189 mg/dL); LDL cholesterol level ≥4.921 mmol/L (190 mg/dL)	10-y risk >20%; DM
Antihypertensives	10-y CVD mortality ≥10% and BP ≥140/90 mm Hg; consider if 10-y risk of 5%–10% and BP ≥140/90 mm Hg; type 1 DM or type 2 DM and BP ≥140/85 mm Hg; age >60 y and systolic BP >150 mm Hg or age >80 y and systolic BP >160 mm Hg; BP ≥180/110 mm Hg	NR	5-y FRS ≥15%; FRS 10%–15% and BP persistently ≥160/100 mm Hg or FHx of premature CVD or high-risk ethnicity; consider if FRS <10% but BP persistently ≥160/100 mm Hg	NR	BP ≥140/90 mm Hg; >130/85 mm Hg in CKD and DM
Intensive lifestyle counselling	10-y CVD mortality >1% or LDL cholesterol level >2.59 mmol/L (100 mg/dL)	10-y CHD/stroke/TIA risk ≥10%	5-y CHD/stroke risk ≥10%	10-y CHD/stroke risk ≥7.5% and LDL cholesterol level of 1.813–4.895 mmol/L (70–189 mg/dL); type 1 or 2 DM; LDL cholesterol level	NR

				≥4.921 mmol/L (190 mg/dL)	
High-risk monitoring	NR	NR	Monitor risk profile according to clinical context if 5-y CHD/stroke risk ≥15%; monitor risk profile every 6–12 months if 5-y CHD/stroke risk is 10%–15%	NR	NR
Screening intervals	NR	Further risk assessment on an on-going basis; 5 yearly per National Service Framework	Further risk assessment every 2 y if 5-y CHD/stroke risk <10%	Further risk assessment every 4–6 y if 10-y CHD/stroke risk <7.5%	NR

Abbreviations: BP = blood pressure; CEA = cost-effectiveness analysis; CHD = coronary heart disease; CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; FHx = Family history; FRS = Framingham Risk Score; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NA = not applicable; NR = not reported; TIA = transient ischaemic attack.

* Formal screening test (included in the prediction model).
† Additional screening test.
‡ In selected persons who are not in 1 of the 4 main statin benefit groups and for whom a decision to initiate statin therapy is otherwise unclear, additional factors may be considered to inform treatment decision-making. These factors include a primary LDL cholesterol level ≥4.144 mmol/L (160 mg/dL) or other evidence of genetic hyperlipidaemias; a first-degree relative with premature atherosclerotic CVD; a high-sensitivity C-reactive protein level >19.0 nmol/L; a coronary artery calcium score ≥300 Agatston units or categorisation in the ≥75th percentile for age, sex, and ethnicity; an ankle–brachial index <0.9; or an elevated lifetime risk for atherosclerotic CVD.
§ Novel biomarkers have only limited additional value when added to CVD risk assessment with the
Systematic Coronary Risk Evaluation algorithm in limited cases.
|| According to the UKPDS (United Kingdom Prospective Diabetes Study) tool.

Table 8. Recommendations for the screening for dysglycaemia in 7 guidelines

Variable	DAGDC	CDA	ADA	USPSTF	NICE PH38	CTFPHC	ESC
Country	Australia	Canada	United States	United States	United Kingdom	Canada	Europe
Year	2009	2013	2016	2015	2012	2012	2013
AGREE II rigor score, %	87	83	82	76	73	68	66
Method to evaluate evidence	Systematic review	Systematic review	Systematic review	Systematic review	Systematic review	Systematic review	Systematic review
Methods to formulate recommendations	Formal consensus	Formal consensus	Formal consensus	Consensus	Consensus	Formal consensus	Formal consensus
Consideration of costs	Review of CEAs	Review of CEAs	Review of CEAs	Review of CEAs	Review of CEAs	Systematic review of published literature/performed CEA	NR
Target group	All adults aged ≥40 y or Aboriginal and Torres Strait Islanders ≥18 y	All adults aged ≥40 y or high-risk groups using risk calculator	All adults over 45 y or all adults with BMI ≥25 kg/m^2 (or ≥23 kg/m^2 in Asian Americans) and 1 additional DM risk factor	Adults aged 40-70 y with BMI ≥25 kg/m^2	>40 y; 25-39 y South Asian, Chinese, black with high-risk scores	Asymptomatic adults	FINDRISC ≥15/26 (high risk for DM)
Strategy	Opportunistic screening	Opportunistic screening/case finding	Opportunistic screening/case finding	Opportunistic screening	Opportunistic screening including during NHS Health Checks; case finding/record-based	Opportunistic screening	Case finding/patient completed questionnaire-based information
Strength of recommendation	For	For	For	For—moderate overall benefit for screening and implementing intensive lifestyle intervention	For—only in high-risk groups	For—only in high-risk groups	For—only in high-risk group
Prediction model	Diabetes risk assessment, e.g. AUSDRISK ≥15 high risk	Diabetes risk assessment	Diabetes risk assessment	NR	Diabetes UK score	FINDRISC, 10-y DM risk or other validated risk score (e.g., CANRISK)	FINDRISC, 10-y DM risk

Risk factors							
Age	*	*	*	*	*	*	*
Sex	*			*	*	*	*
Blood pressure			*				*
Total cholesterol level							
HDL cholesterol level	†	*	*				
Total cholesterol–HDL cholesterol ratio				*			
Smoking	*		*	*			
Glucose levels	†	* (or haemoglobin A_{1c})	*		† (or haemoglobin A_{1c})	† (or haemoglobin A_{1c})	
Underlying risk factors							
Overweight/obesity	*	*	*	*	*	*	*
Physical inactivity	*		*	*		*	*
Atherogenic diet						*	
Family history of premature CVD		*	*				
Genetic/racial factors	*	*	*	*	*	*	
Antihypertensive therapy	*	*	*	*		*	*
Emerging risk factors							
TG levels	†	*	*				
Renal function							
Thresholds							
Aspirin	NR	Not routinely recommended. May be used in presence of other CVD risk factors	Consider if DM with 10-y ASCVD risk ≥10%. Consider aspirin in women ≥50 y. Clinical judgment required for antiplatelet use if <50 y with multiple risk factors and 10-y ASCVD risk 5-10%	Not recommended	NR	NR	Consider in high-risk DM patients on an individual basis
Statins	NR	If found diabetic in men >40 y; <40 y with microvascular complications,	Consider moderate- or high-intensity statin if DM and 40-75 y, DM and >75 y or if DM and <40 y	NR	NR	NR	Very high risk; severe renal disease, 1 other CVD risk factor or target organ damage and

		diabetes for >15 y and age >30 y	with ≥1 other ASCVD risk factors (family history of premature ASCVD, hypertension, smoking, overweight or obese, LDL cholesterol >100 mg/dL; high-intensity statin if 40-75 y with additional ASCVD risk factor. Moderate- to high-intensity statin if >75 y and additional ASCVD risk factors				LDL cholesterol >70 mg/dL; T2DM and LDL cholesterol >100 mg/dL
Antihypertensives	NR	If found diabetic and BP >130/80 mm Hg	DM and BP >140/90 mm Hg	NR	NR	NR	DM and BP >140/85 mm Hg
Intensive lifestyle counselling	IFG; IGT	IFG; IGT	IGT or IFG or haemoglobin A_{1c} 5.7-6.4 mmol/L	For those with abnormal blood glucose (IGT, IFG or diabetes); BMI >25 kg/m^2 and additional CVD risk factors; BMI ≥30 kg/m^2	High risk and IFG/haemoglobin A_{1c} 42-47	NR	High risk for DM
High-risk monitoring	Yearly if IFG/IGT	Yearly if IFG/IGT	Annual screening if IGT or IFG or haemoglobin A_{1c} 5.7-6.4 mmol/L	NR	Every year if high risk and IFG or haemoglobin A_{1c} 42-47 mmol/mol	Annual screening if very high risk (e.g., FINDRISC >20)	Depending on clinical context
Screening intervals	3 y; annual if IFG/IGT	3 y; annual if IFG/IGT	3 y if normal; 6-12 months postpartum if GDM, then every 3 y if normal	3 y if normal glucose levels	At least 5 y starting with risk assessment tool for low risk; 3 yearly for those at moderate risk for diabetes	3-5 y	NR

Abbreviation: ADA = American Diabetes Association; AGREE = Appraisal of Guidelines for Research and Evaluation; ASCVD = atherosclerotic cardiovascular disease; AUSDRISK = Australian Type 2 Diabetes Risk Assessment Tool; BMI = body mass index; BP = blood pressure; CANRISK = Canadian Diabetes Risk Questionnaire; CDA = Canadian Diabetes Association; CEA = cost-effectiveness analysis; CTFPHC = Canadian Task Force on Preventive Health Care; CVD = cardiovascular disease; DAGDC = Diabetes Australia Guideline Development Consortium; DM = diabetes mellitus; ESC = European Society of Cardiology; FINDRISC = Finnish Diabetes Risk Score; GDM = gestational diabetes mellitus; HDL = high-density lipoprotein; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; LDL = low-density lipoprotein; NHS = National Health Service; NICE PH38 = National Institute for Health and Care Excellence public health guidance 38; NR = not reported; T2DM = type 2 diabetes mellitus; TG = triglyceride; USPSTF = U.S. Preventive Services Task Force.

* Formal screening test (included in the prediction model).
† Additional screening test.

Table 9. Recommendations for the screening for dyslipidaemia in 2 guidelines

Variable	ESC	AACE
Country	Europe	United States
Year	2011	2012
Appraisal of Guidelines for Research and Evaluation II rigor score, %	72	64
Method to evaluate evidence	Systematic review	Review of published systematic reviews and RCTs; literature identified by panel members
Methods to formulate recommendations	Formal consensus	Formal consensus
Consideration of costs	NR	Review of CEA studies
Target group	DM, hypertension, smokers, BMI ≥30 kg/m^2, FHx of premature CVD, FHx of familial hypercholesterolemia, CKD, chronic inflammatory conditions, men >40 y, women >50 y or postmenopausal	Aged ≥20 y
Strategy	Opportunistic screening/case finding	Opportunistic screening/case finding
Strength of recommendation	For	For
Prediction model	SCORE, general ASCVD mortality at 10 y	Framingham/Reynolds Risk Score, CHD/stroke at 10 y
Risk factors		
Age	*	*
Sex	*	*
BP	*	*
Total cholesterol level	*	*
LDL cholesterol level	*	*
HDL cholesterol level	*	*
Total cholesterol–HDL cholesterol ratio	*	*
Smoking	*	*
Underlying risk factors		
Family history of premature CVD		*
Diabetes		*
Emerging risk factors		
TG levels	*	†
Apolipoprotein/lipoprotein levels	†	†
Glucose therapy for insulin resistance		*
Prothrombotic markers		‡
C-reactive protein level		‡
Thresholds		

Aspirin	NR	NR
Statins	10-y CVD mortality risk ≥10% and LDL cholesterol level ≥70 mg/dL; 10-y CVD mortality 5%-9% and LDL cholesterol level ≥100 mg/dL; (type 1 DM or type 2 DM) and LDL cholesterol level ≥70 mg/dL; very high CV risk (type 2 DM, type 1 DM with target organ damage, CKD)	LDL cholesterol to <100 mg/dL for those at risk of CHD, if average or elevated LDL; other parameters based on target levels. Lipid goals should be personalised by levels of risk
Antihypertensives	NR	NR
Intensive lifestyle counselling	10-y CVD mortality >1% or LDL cholesterol >100 mg/dL	10-y risk ≥20%
High-risk monitoring	NR	NR
Screening intervals	NR	Every 5 y if aged ≥20 y, but more frequent if other CHD risk factors or FHx of premature CHD, every 1-2 y if aged ≥45 y male or aged ≥55 y female with more frequent assessment if multiple other risk factors present

Abbreviation: AACE = American Association of Clinical Endocrinologists; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CEA = cost-effectiveness analysis; CHD = coronary heart disease; CKD = chronic kidney disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; ESC = European Society of Cardiology; FHx = family history; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NR = not reported; RCT = randomised, controlled trial; SCORE = Systematic Coronary Risk Evaluation; TG = triglyceride.

* Formal screening test (included in the prediction model).
† Additional screening test.
‡ In selected persons who are not in 1 of the 4 main statin benefit groups and for whom a decision to initiate statin therapy is otherwise unclear, additional factors may be considered to inform treatment decision-making. These factors include primary LDL cholesterol level ≥160 mg/dL or other evidence of genetic hyperlipidaemias; first-degree relative with premature ASCVD; high-sensitivity C-reactive protein >2 mg/L; coronary artery calcium score ≥300 Agatston units or ≥75th percentile for age, sex, and ethnicity; ankle–brachial index <0.9; or elevated lifetime risk for ASCVD.

Table 10. Recommendations for the screening for hypertension in 3 guidelines

Variable	CHEP	USPSTF	CTFPHC
Country	Canada	United States	Canada
Year	2015	2015	2013
AGREE II rigor score, %	90	79	78
Method to evaluate evidence	Systematic review	Systematic review	Systematic review
Methods to formulate recommendations	Formal consensus	Consensus	Consensus
Consideration of costs	NR	NR	NR
Target group	All adults	≥18 y with increased risk for high BP: high-normal BP (130-139/85-89 mm Hg), overweight or obese, and African Americans	≥18 y
Strategy	Opportunistic screening at "appropriate visits"	NR	Opportunistic screening at "appropriate visits"/case finding
Strength of recommendation	For	For	For
Prediction model	SCORE-Canada, general ASCVD mortality at 10 y	NR	NR
Risk factors			
Age	*	*	*
Sex	*		
BP	*	*	*
Total cholesterol level	*		
HDL cholesterol level	*		
Smoking	*		
Underlying risk factors			
Overweight/obesity	*	*	
Physical inactivity	*		
Atherogenic diet	*		
Family history of premature CVD			
Genetic/racial factors		*	*
Diabetes	*		
Emerging risk factors			
Renal function	*		
Subclinical atherosclerosis	LVH/resting ECG		LVH/resting ECG
Thresholds			
Aspirin	Consider if ≥50 y and hypertensive	NR	NR
Statins	If ≥3 of: male/≥55	NR	NR

	y/smoking/type 2 DM/total cholesterol–HDL cholesterol ratio ≥ 6/FHx CVD/LVH/ ECG abnormalities/microalbuminuria/PVD		
Antihypertensives	If found diabetic and BP >130/80 mm Hg; high risk for diabetes and BP >140/90 mm Hg; low risk and BP >160/100 mm Hg; ≥80 y and systolic BP >160 mm Hg	NR	NR
Intensive lifestyle counselling	In all with hypertension	NR	NR
High-risk monitoring	Annual if BP high normal (≥130/85 mm Hg)	Annually if ≥40 y and at increased risk for high BP	Annual if BP high normal (≥130/85 mm Hg)
Screening intervals	NR	Annually if ≥40 y and at increased risk for high BP. Every 3 to 5 y if 18-39 y with normal BP (<130/85 mm Hg) and not other risk factors.	Further risk assessment based on clinical judgment

Abbreviation: AGREE = Appraisal of Guidelines for Research and Evaluation; ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CHEP = Canadian Hypertension Education Program; CTFPHC = Canadian Task Force on Preventive Health Care; CVD = cardiovascular disease; DM = diabetes mellitus; ECG = electrocardiography; FHx = family history; HDL = high-density lipoprotein; LVH = left ventricular hypertrophy; NR = not reported; PVD = peripheral vascular disease; SCORE = Systematic Coronary Risk Evaluation; USPSTF = U.S. Preventive Services Task Force.

* Formal screening test (included in the prediction model).

Areas of agreement

Recommendations from 16 of the 17 guidelines supported CVD risk assessment, either as the primary approach (5 guidelines) or a secondary step (11 guidelines). There was a consensus on how screening tests should be administered in the general population. A selective screening system based on knowledge of prior patient characteristics (record-based screening) or used during non-preventive patient visits (case finding or opportunistic screening) was advocated in 14 of the 17 guidelines. Two guidelines did not explicitly specify a screening method (1 from the Centre for Disease Control and Prevention [CDC]/AHA and another from the USPSTF on hypertension).

Authors of most guidelines recommended integrating age, sex, smoking, BP, and lipid levels into CVD risk assessment by using prediction models. However, there was no consensus on which prediction model to use. All 7 dysglycaemia guidelines recommended selecting individuals at high risk for type 2 diabetes mellitus through formal short-term (10-year) or informal diabetes risk algorithms based on antecedent risk factors, along with the often-used threshold of 40 years. Diabetes risk algorithms were also used to decide whether further formal diabetes screening with blood testing was required. The most commonly mentioned risk assessment tool for diabetes was the Finnish Type 2 Diabetes Risk Assessment Form or a modified version tailored to the country implementing it.

Most guidelines agreed on the need to consider ethnicity as a risk factor for CVD and cited specific high-risk ethnic groups. The UK (NICE) and USA (ACC/AHA) guidelines use ethnicity in algorithms for global CVD risk score. The UK-based CVD risk score calculator (QRISK2) advocated by NICE includes several ethnic groups. In the dysglycaemia guidelines, the UK, Australian, and Canadian diabetes risk assessment questionnaires all incorporate ethnicity in the prediction of type 2 diabetes onset.

There was a consensus on the limited role of novel biomarkers (for example, C-reactive protein, Apo lipoprotein, and prothrombin markers) and markers of subclinical atherosclerosis (for example, ankle–brachial pressure index, coronary artery calcium score, and carotid ultrasonography result). The ESC and ACC/AHA are the 2 main guidelines that consider the use of these markers in limited situations. The ACC/AHA suggests that in selected individuals who are not in 1 of the 4 statin benefit groups and for whom a decision to initiate statin therapy is otherwise unclear, additional factors may be considered to inform treatment decision-making. These factors include a high-sensitivity C-reactive protein level greater than 2 mg/L; coronary artery calcium score of 300 Agatston units or greater or categorisation in the 75th percentile or higher for age, sex, and ethnicity; and an ankle–brachial index less than 0.9. The ESC states that routine use of novel biomarkers is not recommended for refinement of CVD risk stratification. Carotid ultrasonography for atheroma detection, measurement of coronary artery calcification, and the ankle–brachial index may be considered as

risk modifiers in CVD risk assessment but are only useful in persons near thresholds for risk categorisation.

Thresholds for initiating treatment are predominantly based on 5- or 10-year absolute risk for CVD or the combination of age and additional CVD risk factors. There were often exceptions made for persons with extreme levels of a single risk factor or those considered to be in a high-risk category (such as those with kidney disease or diabetes mellitus).

Guidelines authors advocate a conservative approach to aspirin use for primary prevention. Of the 8 guidelines that make recommendations on aspirin use, 3 do not recommend routine use for primary prevention, 3 of the dysglycaemia guidelines recommend considering aspirin therapy but only in the presence of additional factors putting patients in a high-risk category, and only 2 guidelines based the recommendation on age alone. The CDC/AHA guideline, which is the only guideline in this review that is sex-specific, makes recommendations for women only and suggests aspirin use in those older than 65 years; however, the Canadian Hypertension Education Program (Hypertension Canada) recommends its use in hypertensive patients older than 55 years. Both guidelines have the caveat that aspirin use should be guided by individual factors. The latest USPSTF guideline on aspirin use for primary prevention, in contrast, recommends aspirin for all adults aged 50 to 59 years who have a 10-year CVD risk of 10% or greater, are not at increased risk for bleeding, and have a life expectancy of more than 10 years [189].

There was a consensus on the importance of addressing lifestyle factors in all target groups independent of pharmacotherapy. Recommendations on who should receive intensive lifestyle counselling differed among the guidelines, with no consensus based on global risk scores. However, the dysglycaemia guidelines advocate that all persons at high risk for diabetes (impaired fasting glucose or impaired glucose tolerance) should receive intensive lifestyle intervention to prevent its onset.

There were no firm statements regarding screening intervals. However, the total CVD risk guidelines advocated rescreening but intervals varied from 2 to 6 years in low-risk persons. Recommended dysglycaemia screening intervals in persons without evidence of diabetes was 3 to 5 years. One dyslipidaemia guideline recommended screening every 5 years for adults younger than 45 years and every 1 to 2 years for those older than 45 years. For those identified as having impaired fasting glucose or impaired glucose tolerance, the consensus was that subsequent annual monitoring should be done.

Areas of disagreement

There was no consensus on the target population for screening. The US guidelines for total cardiovascular risk (ACC/AHA and CDC/AHA), dyslipidaemia (American Association of Clinical Endocrinologists), and dysglycaemia (American Diabetes Association) along with the Canadian guidelines for dysglycaemia (Canadian Task Force on Preventive Health Care) and hypertension (Canadian Hypertension Education Program and Canadian Task Force on Preventive Health Care) advocate screening at a younger age (20 years). The European, UK, and Australian guidelines advocate an older target population of persons older than 40 years.

Although guidelines authors mostly agree on the use of prediction models as part of the risk assessment process or in guiding therapy, there is no consensus on which model to use, particularly for total CVD risk. All 5 total CVD risk guidelines use different calculators, including the QRISK2 (NICE), Systematic COronary Risk Estimation (ESC), 5-year FRS (National Vascular Disease Prevention Alliance), Pooled Cohort Equation (ACC/AHA), and 10-year FRS or Reynolds Risk Score (CDC/AHA). These risk models differ in the end points and risk factors they consider in their development.

Guidelines on total cardiovascular risk differ about when to initiate statin treatment. There was no consensus about CVD risk threshold, although direct comparison is challenging because all 5 guidelines used different risk prediction models. The more recent ACC/AHA and NICE recommendations on total cardiovascular risk have lowered their threshold for initiation of statins. However,

these 2 updated guidelines have also changed the CVD risk equations that they now use, which makes direct comparison to older thresholds difficult because of different data sets or end points that are used in developing the algorithms. The NICE guideline now advocates for the QRISK2 algorithm, and the ACC/AHA now advocates for the Pooled Cohort Equation for predicting general CVD. Previously, they both used the FRS. The 2016 ESC guideline has maintained the same statin thresholds as recommended in the 2012 version. Statin recommendations were made in 3 of the 7 dysglycaemia guidelines, with only 1 using age older than 40 years as the sole deciding factor in persons diagnosed with diabetes.

Recommendations on initiating antihypertensive medication varied, and there was no consensus on global risk or BP thresholds. However, most of the guidelines agreed on the importance of considering antihypertensive medications in diabetic patients but again varied on the BP threshold used for guidance.

There was no consensus on the use of lifetime or relative risk in young adults to overcome the problem of 5- to 10-year time horizons for predictions. The ACC/AHA advocates the use of lifetime risk to guide intensive lifestyle intervention in young adults. The ESC recommends the use of relative risk charts for informing young adults of risk, whereas the NICE guideline generally advises against using lifetime risk tools.

There was no agreement among the guidelines on which subclinical atherosclerosis screening test to use. Only 2 guidelines on total CVD risk (ACC/AHA and ESC) suggested using imaging tests (coronary artery calcium scoring and carotid ultrasonography for atheroma detection), but only in selected individuals to guide management decisions. The Australian guideline (National Vascular Disease Prevention Alliance) was the only total CVD guideline to recommend assessing LVH in the primary risk assessment.

Discussion

I identified 21 guidelines, of which 17 were rigorously developed, on cardiovascular screening interventions that could be done within a cardiovascular

health check program. The aim of this systematic review was not to provide a comprehensive integration of the guidelines but rather a summary of rigorously developed national and international guidelines available to physicians in the form of a quick reference, which allows for easy comparison. There was a consensus on performing CVD risk screening and using prediction models for risk stratification and guiding treatment. The guidelines also agreed on the use of relatively simple risk markers, including age, sex, ethnicity, and smoking history. Novel biomarkers or markers of subclinical atherosclerosis are generally not recommended, except in a very select subgroup of individuals. The guidelines advocate a conservative approach to aspirin initiation for primary prevention, and there was a general agreement on intervals for repeated screening. Guidelines on selection of the ideal target population, which risk prediction model to use, and which thresholds to use to initiate statin or antihypertensive treatment differ.

I performed a broad search using major medical publication repositories, guideline library Web sites, and individual guideline development group Web sites (through manual search). In contrast to our previous article, this review only summarises recommendations from guidelines. Other reports, such as position and scientific statements, are not in the remit of the AGREE II instrument and were excluded. All of the guidelines included in this review were published in the past 7 years and represent the most recent recommendations. None of the current 21 guidelines were included in the previous review from our group[89].

Guidelines generally recommend basing management decisions on global cardiovascular risk that considers multiple risk factors. However, they differ with regard to risk thresholds. This is partly because the risk models advocated in the guidelines vary over data set use, the predictors used, and their end points. The Systematic COronary Risk Estimation model (ESC) uses only hard end points of CVD mortality, whereas the FRS (CDC/AHA and the National Vascular Disease Prevention Alliance) uses the broadest end points, consisting of coronary death, myocardial infarction, coronary insufficiency, angina, ischaemic stroke, haemorrhagic stroke, transient ischaemic attack, peripheral artery disease, and heart failure. Furthermore, the 7.5% risk threshold for initiating a statin used by the ACC/AHA is based on the newer Pooled Cohort Equation, which uses the 10-

year nonfatal myocardial infarction, CHD death, or stroke end points[34]. This variability can lead to the same groups receiving different treatment, makes comparison among several health care systems challenging, and could also lead to health care inequality. The AHA/ACC guidelines, for example, would recommend statins for nearly all men and two thirds of women older than 55 years. This exceeds the proportion that would be eligible based on other guidelines, such as the ESC, when tested in a European cohort[207]. Standardisation of various risk scoring systems, with validation and calibration, may help improve clinical outcomes in persons at risk for CVD[208]. However, risk scoring systems would need to be developed or updated for different countries because of country- and region-specific differences in event rates and mortality.

Programs attempting to provide population-based interventions that determine the overall effect achieved face many challenges. The diversity in CVD guidelines may partly reflect the uncertainty of the benefits of screening. Although evidence supports the effectiveness of particular interventions to appropriate persons, screening programs face such difficulties as achievement of sufficiently high uptake rates to invitations, ability to deliver effective interventions, and patient adherence to recommendations.

Most guidelines recommended a selective screening strategy, with some newer guidelines advocating a lower threshold for initiating treatment, such as statin therapy, and citing recent meta-analysis and the reduced costs of statins due to patent expiry as the main reasons for this shift [29]. Thresholds used for determining high risk are often arbitrary and at best decided on by mathematical modelling. Studies that show modest benefit have mainly been based on improvements in surrogate markers rather than CVD events, with inherent limitations [209].

A MEDLINE search identified 4 previous systematic reviews, published between 1 January 2009 and 30 June 2016, that were relevant to our study (Appendix). Two were from our group, including our previous (now out-dated) review, and another focused on guidelines of screening only for peripheral vascular disease [89,210]. The remaining 2 publications were limited to guidelines on primary CVD prevention in older adults (searches up to December 2013) or the diagnosis, assessment, and

management of hypertension (searches up to September 2011)[211]. This systematic review represents contemporary guidelines with a broad inclusion of conditions eligible for cardiovascular risk assessment in apparently healthy adults and an assessment of the guidelines' rigor of development.

Compared with our previous publication from 6 years ago, the target populations, risk prediction models, and their consequences are still areas of disagreement across guidelines [89]. Over the past 6 years, there has been a trend toward advocating a lower threshold for initiating intensive lifestyle modification and statin therapy. Risk prediction models have been updated with a move away from the FRS, which previously predominated. Guidelines have a more conservative approach to aspirin, with most generally advocating against it for primary prevention. The use of tests for assessment of subclinical atherosclerosis has been further restricted.

The optimal strategy for systematic screening of the apparently healthy population remains to be found. Some groups advocate continuing with the current strategy of screening with the aim of trying to mould it into a system that eventually shows benefit, whereas others are asking for the programs to be halted until such a time that the evidence of benefit justifies the resources invested [212,213]. Recent publications addressing some of these gaps and future research in identifying the most effective strategies will help shape future guideline recommendations [214-216].

Some limitations could bias our findings and limit generalisability. Only guidelines developed by Western national or international medical organisations were reviewed. I controlled for selection bias by having a comprehensive search strategy, as previously generated with a librarian, and the articles were selected and appraised by 2 independent researchers. However, researchers were not blinded to the organisation names or countries of origin. Of note, I considered the guideline development process but did not assess the clinical validity of recommendations or review them for specific lifestyle interventions because it was beyond the scope of this review.

Conclusion

Cardiovascular screening guidelines still have considerable discrepancies, with no consensus on optimum screening strategies or treatment threshold. Physicians should assess the strength of the recommendations and the level of evidence to decide which of the recommendations they should implement.

Chapter 6 - Lifestyle intervention for reducing total cardiovascular risk: A systematic review of primary prevention guidelines

Preamble

In this chapter I present the findings from a systematic review of the current lifestyle recommendations for primary prevention of CVD advocated by authors of guidelines. The rationale was to identify what lifestyle interventions to recommend to study participants during the face-to-face advice visit and what to incorporate in the HAPPY London website for those receiving e-coaching.

Abstract

Background: CVD remains one of the main causes of morbidity and mortality globally. This review identifies lifestyle advice and interventions from recent guidelines on primary prevention of CVD and highlights the similarities and differences.

Objective: To systematically review current guidelines on screening for total cardiovascular risk and their recommendations on lifestyle advice or intervention in order to guide lifestyle counselling in primary prevention programmes.

Data sources: Guidelines published in the English language between May 3, 2009 and November 20, 2015 were identified using MEDLINE, CINAHL and guideline repositories including G-I-N International Guideline Library, National Guidelines Clearing-house, National Library for Health, Canadian Medical Association InfoBase.

Study selection: Guidelines on primary prevention of CVD that contained recommendations for lifestyle advice and interventions from Western countries were included. Two independent reviewers assessed titles and abstracts.

Data extraction: Two reviewers independently assessed rigor of guideline development and one extracted the recommendations.

Results: Of the 3330 titles identified, 6 met our selection criteria. The guidelines were generally developed with considerable rigor as assessed by the AGREE II criteria (score range 45-86%). The guidelines all agreed on the importance of lifestyle and were very similar in recommendations for smoking cessation, limiting intake of saturated fat, salt, avoiding trans-fat and sugar with particular mention of sugar sweetened beverages. Guidelines generally agreed on recommendations for physical activity levels, and on a diet that is rich in fruit, vegetables, fish and wholegrain. They differed, however, on recommendations regarding red meat and alcohol.

Conclusions: The importance of lifestyle advice and interventions in the primary prevention of CVD is very clear. There is general consensus in the guidelines assessed on many lifestyle factors and these should be included as an integral part of risk reduction programmes.

Background

CVD is a major cause of death worldwide. In England and Wales for example, it accounts for about one-third of all deaths [217]. Despite reductions in death from CVD over the past 3-4 decades, it still remains a leading cause of death and a major cause of morbidity leading to quality of life decline with 180,000 UK deaths in 2010 due to CVD and of these 46,000 occurred before the age of 75 years. CVD also has important financial implications and was estimated to cost the NHS in England about £6.8 billion in 2013[218]. CVD is strongly associated with age and mostly affects those over 50 years of age. Environmental factors identified as driving the epidemic of CVD include smoking, high calorie diets, saturated fats, and high salt intake, in conjunction with low intake of fruit and vegetables and sedentary lifestyles [4]. It is estimated that about 60% of the CVD mortality decline over the 2 decades since the 1980's was attributable to a reduction in major CVD risk factors, primarily smoking. The remaining reduction was attributed to pharmacotherapy[219]. A more recent analysis confirms that improvements in a number of modifiable risk factors including smoking, cholesterol and BP can explain much of the reduction in CHD mortality [220].

Lifestyle intervention plays an important role in prevention of a number of CVD end points and its promotion has been emphasised in many CVD prevention guidelines [17,20,31,153,221]. Despite this, most people in many Western countries do not meet the recommendations for diet and physical activity despite known health benefits including future CVD risk reduction [222]. Prevention of CVD is a rapidly evolving field and the potential for long term health care benefits from timely, personalised risk factor assessment and intervention has been recognised [17]. The human and economic arguments in favour of CVD prevention were estimated by NICE as overwhelmingly positive, and other committees hold very similar views [58,223]. Prevention strategies are now predominantly recommending risk stratification based on absolute 10-year CVD risk prediction to guide management.

A systematic review from the USPSTF concluded that diet and physical activity behavioural counselling in persons with risk factors for CVD resulted in consistent improvements across various intermediate health outcomes up to 2 years follow

up [222]. The recent ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk disease (ASCVD) in adults emphasised that lifestyle modification remains a critical component of health promotion and ASCVD risk reduction, both prior to and in concert with the use of cholesterol lowering drug therapies [30]. Healthy diet or lifestyle modifications were recommended as background therapy in published RCTs of cholesterol lowering drug therapy.

The aim of this systematic review was to identify the similarities and differences between recent guidelines addressing total CVD risk reduction in primary prevention to guide clinicians and other health care professionals that are involved in primary prevention programmes and counselling.

Methods

Data sources and guideline selection

I conducted a systematic review, using our search strategy outlined in chapter 5, for guidelines containing recommendations for lifestyle interventions for a primary prevention population [89]. I looked at guidelines that dealt with total cardiovascular risk rather than specific to a single condition such as hypertension or hypercholesterolaemia alone.

I performed a systematic literature search to identify appropriate guidelines [89]. I searched for published guidelines using MEDLINE and CINAHL between May 3, 2009 and November 20, 2015. I supplemented this by using the following guidelines specific databases; 1) The National Guideline Clearinghouse (US), 2) National Library for Health on Guidelines Finder (UK), 3) Canadian Medical Association InfoBase (Canada), and 4) G-I-N International Guideline Library (http;/www.g-i-n.net). I also carried out a search of a number of websites of guidelines development organisations. I restricted our search to national guidelines from the US, Canada, the UK, Australia and New Zealand and other international guidelines written in English.

Titles and abstracts were assessed by 2 independent reviewers (Vinicius Bicalho and I). Articles were excluded if both reviewers agreed they were not eligible. Discrepancies between reviewers were resolved by consensus. Both reviewers performed the final selection for full data extraction.

I utilised the 23-item Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument to determine the rigor of development for each of the guidelines [224]. This domain of the AGREE II instrument considers the reporting of 1) method to search for evidence, 2) criteria for selection of evidence, 3) strengths and limitations of the body of evidence, 4) methods for formulating the recommendations, 5) health benefits, side effects, and risks, 6) explicit link between recommendations and the evidence, 7) procedures for external expert peer review, and the 8) updating process. Two reviewers (Claudia van Waardhuizen and I) independently rated the 8 items on a 7-point Likert scale in accordance with the instructions of the AGREE II committee.

Average rigor scores were obtained by expressing the sum of the individual scores as a percentage of the maximum possible score and reproducibility of the 2 reviewers scores was very good, with an interclass correlation of 0.80 (comparing the agreement of the total rigor of development score obtained by the two reviewers (Claudia van Waardhuizen and I, for the guidelines included in this chapter). Guidelines were ranked according to their scores. Editorial independence from the funding body, external funding and disclosure of relationships with industry was also assessed.

Recommendation Extraction

I extracted all the relevant recommendations from the guidelines. General lifestyle advice was the main emphasis of the data extraction. A recommendation matrix was produced. The matrix was divided into (1) a methods section, (2) target group and delivery of screening and (3) recommended lifestyle advice.

Results

Of our 3330 titles that the search retrieved, 3295 were excluded as duplicates or following title or abstract review (Figure 49). Of the remaining 35, full article review retained 6 guidelines that met our inclusion criteria (Summary of selected guideline characteristics in Table 11). The guidelines originated from the USA (2 guidelines), UK (2), Australia (1) and Europe (1). Table 12 Contains the recommendation matrix.

Table 11. Characteristics of 6 Guidelines for Total Cardiovascular risk

Guideline	**Organisation Responsible for Guideline Development**	**Country Applied**	**AGREE2 Rigor score, %**	**Conflicts of Interest**
ESC[225], 2012	European Society of Cardiology	Europe	86	SCI*
NICE[31], 2014	National Institute for Health and Clinical Excellence	United Kingdom	86	EI,SCI*†
NHMRC[190], 2012	National Health and Medical Research Council	Australia	85	EI,SCI†
ACC/AHA[20,30,34], 2013	American College of Cardiology	United States	83	SCI*†
CDC[191], 2011	Centres for Disease Control and Prevention	United States	65	EI,SCI*†
BCS[17], 2014	British Cardiovascular Society	United Kingdom	45	SCI*

Abbreviations: AGREE2, Appraisal of Guidelines Research and Evaluation II; EI, editorial independence declared; FIP, funding by industrial partner reported; SCI, statement about conflicts of interest of group members present; UK, United Kingdom

*Relationship with industry is reported by any group member;

† A group member is reported recused when a relevant area is under discussion;

‡ Conflicts of interest only available on request;

§ COI only reported to the group

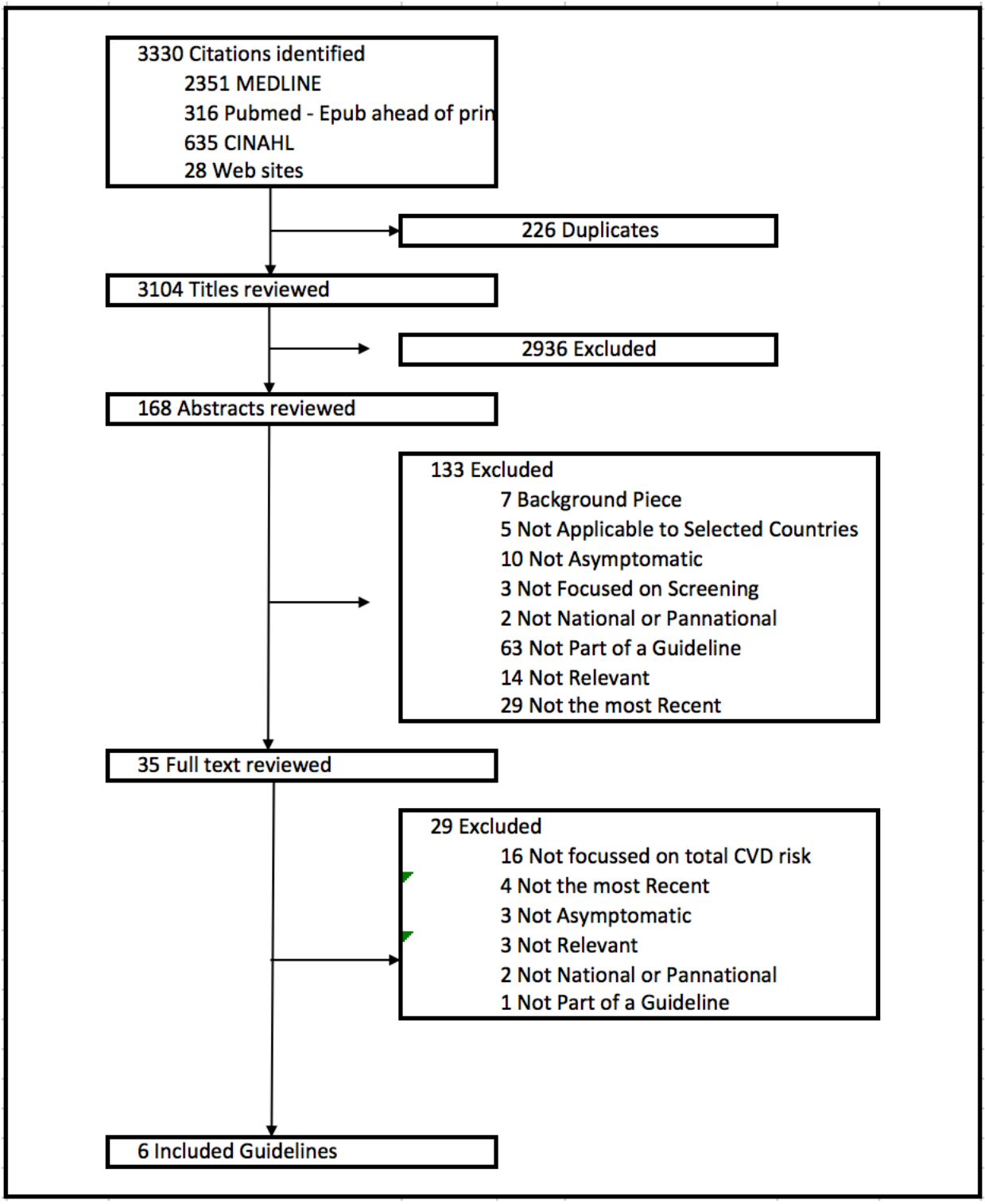


Figure 49. Flow diagram showing search and guideline selection process

Table 12. Lifestyle recommendations for total CVD risk reduction in 6 Guidelines

	NICE	ESC	NVDP	ACC/AHA	CDC/ AHA	BCS
	UK	EUR	Australia	USA	USA	UK
	2014	2012	2012	2013	2011	2014
AGREE 2 Score	86%	86%	85%	83%	65%	45%
Method to evaluate evidence	Systematic review	Systematic review	Systematic review	Systematic review	Systematic review	Review
Methods to formulate recommendations	Formal consensus	Formal consensus	Formal consensus	Formal consensus	Formal consensus and voting	NR
Consideration of costs	Systematic review of published literature/ Performed CEA	Review of CEA studies	Review of CEA studies	Not performed	Review of CEA studies	Review of CEA studies
Target Group	Aged 40-74 (NHS Health Check)	Men > 40-y, Women >50-y or post menopausal		Aged 21 and above	Women >= 20 y	Children and adults
High Risk Group	Type 1 DM, eGFR <60 ml/min/1.73m 2, over 85 years old, QRISK2 >10% at 10 years	DM, > moderate CKD (eGFR < 60mL/min/1.7 3m2), very high levels of individual risk factors, high SCORE risk (≥5%) and are high priority	DM and age >60 years; DM with microalbuminuri a (>20 mcg/min or UACR >2.5 mg/mmol for males, >3.5 mg/mmol for females); Moderate or severe CKD			Diabetes, age >40 years, CKD stages 3–5, Familial Hypercholesterol-aemia or high short term risk as per NICE 2014 (i.e. QRISK2 ≥10%)

		for intensive advice about all risk factors	(persistent proteinuria or eGFR <45mL/min/1.73m2); A previous diagnosis of familial hypercholesterolaemia; SBP >= 180mmHg or DBP >= 110 mmHg; Serum TC >7.5 mmol/L			
Screening Strategy	Opportunistic screening/ case finding/ record based - to identify high risk	Opportunistic screening/ case finding	Opportunistic screening/ case finding	Opportunistic screening/ case finding	NR	Linked to NHS Health Checks Development of a CVD prevention strategy for individuals with low short term but high lifetime risk of CVD
Thresholds						
Behavioural change strategy		Establish CBT (e.g. motivational interviewing) to facilitate lifestyle change. From specialised health care professionals	Offer counselling for smoking cessation. Consider dietary counselling depending on need			Behavioural counselling or group therapy for smoking cessation. Communicating heart age or lifetime risk measure to motivate change

		when ever necessary and feasible. / In high risk individuals use multimodal interventions, integrating education on healthy lifestyle and medical resources, exercise training, stress management and counselling on psychological risk factors				
Intensive Lifestyle Counselling	10-y CHD/stroke/TIA risk ≥10%;	10-y CVD mortality >1% or LDL-C > 100mg/dL.	5-y CHD/stroke risk ≥10%. Adults at higher absolute risk of CVD should be given more frequent and sustained lifestyle advice, support and follow-up to achieve	10-y CHD/stroke risk ≥7.5% and LDL-C 70-189 mg/dL; DM1 or DM2; LDL-C level ≥190 mg/dL.	NR	Diabetes, age >40 years, CKD stages 3–5, Familial Hypercholesterol-aemia or high short term risk as per NICE 2014 (i.e. QRISK2 ≥10%)

			behavioural change.			
High-risk Monitoring	NR	NR	Monitor risk profile according to clinical context if 5-y CHD/stroke risk ≥ 15%. Monitor risk profile every 6-12 months if 5-y CHD/stroke risk 10%-15%.	NR	NR	NR
Screening Intervals	Further risk assessment on an on going basis. 5 yearly as per NSF	NR	Further risk assessment every 2 y if 5-y CHD/stroke risk <10%. Every 6-12 months if risk 10-15%. According to clinical context for those with risk >15%	Further risk assessment every 4-6 y if 10-y CHD/stroke risk <7.5%.	NR	NR
Smoking	Advise all smokers to stop. Offer support and advice and referral to intensive support services to	Avoid all smoking (IB); Avoid passive smoking (IB); Young should be encouraged not to take up smoking (IC); Give all	All smoker should be advised to stop smoking (A); Offer advice about methods to aid smoking cessation including	Not included	Women should be advised not to smoke and avoid environmental tobacco smoke. Provide counselling at each encounter, nicotine replacement, and other pharmacotherapy in	Professional support on stopping smoking at every available opportunity. Self-help material and referral to more intensive support e.g. stop smoking services; Emphasis on early

	those who want to stop. If unable or unwilling to accept referral to intensive support service, then offer pharmacotherapy and Varenicline for smoking cessation	smokers advice to quit and offer assistance (IA)	counselling services, and if assessed as nicotine dependent, nicotine replacement therapy or other appropriate pharmacother-apy should be used	conjunction with a behavioural program or formal smoking cessation program (Class I; Level of Evidence B).	smoking cessation and the diminishing, but still substantial, returns from quitting at an older age; Offer behavioural counselling, group therapy, pharmacotherapy or a combination; NRT, varenicline or bupropion should be offered to those planning to stop smoking; raise awareness of risks of active and passive smoking.
Diet	Advise and support people at high risk of CVD to achieve a healthy diet in line with the Behaviour change: principles for effective interventions (NICE public health guidance 6)	Healthy diet seen as the cornerstone of CVD prevention (IB)	Follow current dietary guidelines for Australian Adults	Women should be advised to consume a diet rich in fruits and vegetables; choose whole-grain, high-fibre foods; consume fish, especially oily fish, at least twice a week; limit intake of saturated fat, cholesterol, alcohol, sodium, and sugar; and avoid trans-fatty acids. (Class I; Level of Evidence B).	Give professional support to consume a diet associated with the lowest cardiovascular risk

Saturated fat	Total fat intake ≤ 30% of total intake, saturated fats ≤7%, dietary cholesterol <300mg/day, replace saturated fats with mono-unsaturated and polyunsaturated fats where possible	Should account for <10% of total energy intake though replacement by polyunsaturated fatty acids. / Trans-unsaturated fatty acids as little as possible, preferably no processed foods and <1% of total energy from natural origin	Diet low in saturated and trans-saturated fats. Low fat dairy products	Reduce per cent of calories from saturated fat; Reduce per cent of calories from trans fat (1A)*	Limit intake of saturated fats to <7% of total energy intake limit and cholesterol to <150mg/day (as found in animal meats, organ meats, eggs etc.). Avoid trans-fatty acids	Intake of saturated fat to <10% of total fat intake (preferably in lean meat and low fat dairy products)/ Replace saturated fat with polyunsaturated fat where possible
Fruit and vegetables	At least 5 portions of fruit and veg per day	200g of fruit per day (2-3 servings); 200g of veg per day (2-3 servings)	Diet rich in fruit and vegetables	Dietary pattern emphasising intake of fruit and vegetables (1A)*^	Diet rich in fruit and vegetables of ≥4.5 cups/day servings	Consume five portions per day of fruit and veg
Fish	At least 2 portions of fish per week, including a portion of oily fish	At least twice a week, one of which should be oily fish	Varied diet rich in fish	Dietary pattern emphasising intake fish (1A)*^	Consume at least twice weekly, especially oily fish	Consume at least two servings of fish (preferably oily) per week
Grains and nuts	Choose	NR	Varied diet rich	Dietary pattern	≥4/week servings per	Consider regular

	wholegrain variety of starches. Eat at least 4-5 portions of unsalted nuts, seeds and legumes per week		in wholegrain cereals, legumes, beans, seeds and nuts	emphasising intake of legumes and nuts (1A)*^	week of nuts legumes and seeds. (E.g. 1/2 cup or 1/2 oz. nuts is one serving) Choose wholegrain high fibre foods	consumption of whole grains and nuts
Salt	Reduce salt intake	< 5g of salt per day	Low salt consumption. Limit salt to <6g/day (approximately 2300 mg sodium)	Lower sodium intake (1A)^; Consume < 2,400 mg of sodium/day; Further reduction to 1,500 mg/day can lower BP more; At least reduce sodium intake by at least 1,000 mg/day to lowers BP (2aB)^	< 1,500 mg/day of sodium	Keep salt consumption <6 g/day
Alcohol intake	Men: not regularly drink > 3-4 units per day, women: not regularly drink > 2-3 units per day. Avoid binge drinking	Limit to 2 glasses per day (20g/day of alcohol) for men and one glass per day (10g/day of alcohol) for women	Limit alcohol intake. Advised to follow the current Australian guidelines to reduce health risks from drinking alcohol (2009)	Not included	≤1/day (e.g. 4 oz. of wine or 12 oz. of beer)	Limit alcohol intake to <21 units per week for men and <14 units per week for women
Oils	Use olive oil, rapeseed oil or	NR	NR	Emphasise pattern including non-	Consumption of omega-3 fatty acids in the form	NR

	spreads based on those oils in food preparation, also as replacement for mono-unsaturated fats.			tropical vegetable oils	of fish or in capsule form (e.g., EPA 1800 mg/d) may be considered in women with hypercholesterolemia and/or hypertriglyceridemia for primary and secondary prevention (Class IIb; Level of Evidence B).	
Sugar	Reduce intake of sugar and food products containing refined sugars including fructose	Avoid sugar sweetened soft drinks		Limit intake of sugars and sugar sweetened soft drinks	≤5/week (≤ 450 kcal/week from sugar sweetened beverages (1 serving is 1 tablespoon of sugar, 1 cup of lemonade)	Avoid sugar sweetened beverages and calorie rich, but nutritionally poor, snacks such as sweets, cakes
Avoid		Sugar sweetened soft drinks (largest single food source of calories in the USA and also important in Europe)		Limit intake of sweets, sugar-sweetened beverages, and red meats.	Limit intake of saturated fat, cholesterol, alcohol, sodium, and sugar; and avoid trans-fatty acids. Avoid macadamia nuts and salted nuts.	Sugar sweetened beverages; Refined carbohydrates, such as white bread, processed cereals; Calorie rich, but nutritionally poor, snacks such as sweets, cakes, and crisps
Meats	NR	NR	Varied diet rich in lean meat and poultry	Dietary pattern emphasising intake poultry	Limit saturated fat intake to <7% as found in fried foods, fat on	Avoid processed meats or commercially

					meat or chicken skin, packaged deserts, cheese etc.	produced foods which tend to be high in salt and TFA
Weight	Offer overweight and obese people appropriate advice and support to work towards achieving and maintaining a healthy weight (in line with the Obesity (NICE guideline 43)	Weight reduction in overweight and obese people is associated with favourable effects on BP and dyslipidaemia, which may lead to less CVD (IA)	Weight loss should be recommended for those who are overweight or obese (B). Limit energy intake to maintain a healthy weight. Ideal weight should be BMI <25 kg/m2 and waist circumference <94 cm in men (<90 cm in Asian men) or <80 cm in women (including Asian women)	Achieve and maintain a healthy weight (As per 2013 Obesity Expert Panel Report)	Women should maintain or lose weight through an appropriate balance of physical activity, caloric intake, and formal behavioural programs when indicated to maintain or achieve an appropriate body weight (e.g., BMI ≥25 kg/m2 in U.S. women), waist size (e.g., ≥35 in), or other target metric of obesity. (Class I; Level of Evidence B).	
Physical activity	At least 150 minutes of moderate intensity aerobic activity or 75 minutes of vigorous intensity	Do 2.5 - 5 hours a week on physical activity or aerobic exercise training of at least moderate	All adults to participate in at least 30 minutes of moderate intensity physical activity on most days of the week,	Engage in 2 h and 30 min per week of moderate-intensity physical activity, or 1 h and 15 min (75 min) per week of vigorous-intensity aerobic physical	Women should be advised to accumulate at least 150 min/week of moderate exercise, 75 min/week of vigorous exercise, or an equivalent combination of moderate- and	An increase in overall levels of sustained physical activity and avoidance of prolonged sedentary behaviour are important for reduction of CVD risk.

	aerobic activity. Or a mix of moderate and vigorous intensity physical activity. * Or exercise at their maximum safe capacity based on co-morbidities or personal circumstances. Agree goals and provide written information about benefits and local opportunities to be active€	intensity or 1-2.5 a week of vigorous intense exercise. Sedentary subjects should be strongly encouraged to start light intensity exercise programmes (IA). / Perform in multiple bouts of >10 mins and evenly spread thought-out the week (i.e. 4-5 days per week) (IIaA)	preferably every day (>2.5 hours/week)(B)	activity, or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity. Aerobic activity should be performed in episodes of at least 10 min, preferably spread throughout the week; 3-4 sessions per week of aerobic physical activity, lasting on average 40 mins per session with moderate to vigorous intensity for those needing to reduce LDL-C and non-HDL cholesterol or BP (2aA)*^	vigorous-intensity aerobic physical activity. Aerobic activity should be performed in episodes of at least 10 min, preferably spread throughout the week (Class I; Level of Evidence B). Women should also be advised that additional cardiovascular benefits are provided by increasing moderate-intensity aerobic physical activity to 5 h (300 min)/week, 2 1/2 h/week of vigorous-intensity physical activity, or an equivalent combination of both (Class I; Level of Evidence B).	/ Emphasise walking, cycling, and other aerobic physical daily activities, at moderate intensity, as part of an active lifestyle, for at least 150 min per week in bouts of ≥10 min, or 75 min per week of vigorous physical activity, or a combination of the two. / Muscle strengthening activities performed on at least two occasions per week.
Exercise training	Perform muscle strengthening activities on 2 or more days of the week that work all major muscles groups.				Women should be advised to engage in muscle-strengthening activities that involve all major muscle groups performed on ⍰2 d/week (Class I; Level of	Incorporating a warm up and cool down period, should be performed at moderate to high intensity two to three times per week for

	*			Evidence B). / Women who need to lose weight or sustain weight loss should be advised to accumulate a minimum of 60 to 90 min of at least moderate-intensity physical activity (e.g., brisk walking) on most, and preferably all, days of the week (Class I; Level of Evidence B).	30–40 min each time. / The mode of exercise should be aerobic and, where possible, continuous allowing for a steady progression in effort —for example, walking programmes, cycling, jogging, swimming. / The time spent exercise training contributes to meeting the 150 min per week physical activity recommendation.
Psychological factors		Assess. Tailored clinical management considered to enhance QOL and CHD prognosis (IIaB)			
Supervised exercise	Refer to programmes such as exercise referral schemes for people who	NR		NR	Those considered at higher risk of CVD: A more structured approach is needed in managing patients, and in all cases

	may need support to change their lifestyle				assessment and specific goal setting, with risk stratification, delivered by professionals skilled in health related exercise, is preferable. /Increase in exercise with community based exercise initiatives are recommended for patients at risk of CVD
Dietary patterns	Mediterranean diet. DASH diet for BP lowering	Mediterranean diets	DASH dietary pattern, the United States Department for Agriculture Food Pattern, or the AHA Diet (1A) *^	DASH- like diet	Dietary advice based on specific dietary patterns, such as the Mediterranean diet or DASH diet, which advocates specific macronutrients or whole foods rather than concentrating on micronutrients

* Advise people who would benefit from LDL lowering; ^ Advise those who would benefit from BP lowering to; €, in line with the Four commonly used methods to increase physical activity (NICE public health guidance 2); *, in line with the national guidance for the general population (see physical activity guidelines for adults at NHS choices);

Abbreviation: ABI = ankle brachial index, CEA = cost-effectiveness analysis, CAC = coronary artery calcium, CHD = coronary heart disease, CKD = chronic kidney disease, CVD = cardiovascular disease, DM = diabetes mellitus, FHx = family history, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, LVH = left ventricular hypertrophy, NHS = National Health Service, NR = not reported, NSF = National Service Framework, SCORE = Systematic Coronary Risk Evaluation, TC = total cholesterol, TG = triglyceride, TIA = transient ischaemic attack, US = ultrasound, y = years

Areas of agreement

Most of the guidelines identified high-risk categories of people that should receive intensive lifestyle counselling. This commonly included presence of diabetes, although no consensus exists as to which group of diabetics (examples include type 1 diabetes and in another diabetes with an additional risk factor such as age>60 or microalbuminauria). For the definition of CKD the most common cut-off was < 60mls/min/1.73m2 with one guideline using <45 mls/min/1.73m2 (NVDP). An elevated calculated risk score was used in some guidelines to identify high risk, although there was no consensus on the risk threshold, primarily due to differences in risk scores used and the end points that the risk scores use in their prediction.

Smoking

There was a consensus regarding the importance of smoking cessation advice. Only the ACC/AHA did not have recommendations on smoking, as it was not in the remit of the guidelines specific clinical questions. Offering additional assistance, including referral to counselling services and pharmacotherapy, was also recommended. Most of the guidelines also specifically mention avoidance of second hand smoke (also termed as environmental/ passive smoking).

Diet

There was a consensus between the guidelines on the importance of dietary advice being a cornerstone of CVD prevention. Further details of the specific elements are provided below.

Saturated fats

There was a common recommendation on the lowering of intake of saturated fats and trans-saturated fats. Three out of the six guidelines specify a recommended percentage for intake with recommended levels below 7% (NICE) or 10% (ESC,

JBS3). The other three guidelines suggest limiting intake but without specifying cut-offs.

Fruit and vegetables

All recommendations state that diets should be rich in fruit and vegetables. Only the ESC makes a distinction in the proportion of intake of fruit vs. vegetables. The UK guidelines recommend five portions of fruits or vegetables (JBS3) or more (NICE) per day. The ESC recommendations refer to 'servings' rather than portions, with between 2-3 servings of both fruit and vegetables per day (equivalent to about 200g of each). The remaining guidelines make general recommendations on a diet rich in fruit and vegetables without specifying cut-offs.

Fish

All guidelines emphasise the recommendation for intake of fish in the diet. Four of the guidelines recommend at least two portions per week with at least one of them being of the oily variety. The remaining guidelines (ACC/AHA and NVDP) generally recommend a diet emphasising the intake of fish without stating any cut-offs.

Grains and nuts

There is a consensus on the recommendation for the consumption of wholegrain in the diet and other sources of fibre. There are general recommendations made encouraging regular intake of wholegrain, beans, seeds and nuts. Only the NICE guideline recommends a specific quantity and suggests at least 4-5 portions of unsalted nuts, seeds and legumes per week. The ESC does not make specific mention of nuts or grains in its recommendations.

Salt consumption

There is a consensus regarding the importance of limiting salt intake in the diet. The most commonly recommended intake of salt was <6g/day (approximately 2,300mg of sodium). The lowest recommendation being from the CDC/AHA

guideline for women of less than 1,500mg of sodium. This cut-off is also mentioned in the ACC/AHA guideline as offering additional BP lowering compared to the 2,400mg of sodium considered the upper limit.

Oils

Most of the guidelines do not make specific recommendations for the types of oils used for cooking. The ACC/AHA recommends the use of non-tropical vegetable oils and NICE recommend the use of olive oil, rapeseed oil or spreads from those oils and as potential replacement for non-saturated fats.

Sugar

There is a general consensus in the recommendations to reduce the amount of sugar in the diet. Particular mention is made on the avoidance, or at least limiting, the intake of sugar sweetened beverages. The NICE guidelines also mention avoiding other food products that contain refined sugars, including fructose.

Weight

There is a general consensus that people who are overweight (most commonly defined as BMI > 25 kg/m^2) or obese (most commonly defined as BMI > 30 kg/m^2) should be offered advice and support to work towards achieving and maintaining a healthy weight. Only the JBS3 has reservations on weight reduction recommendations and mentions that there is limited evidence that weight loss in itself directly reduces CVD risk. It mentions that the effects of weight loss such as BP reduction may have CVD reducing impact. It does, however, recommend weight loss in people with obstructive sleep apnoea/hypopnea syndrome who are overweight as a means to CVD risk reduction.

Physical activity

All guidelines agree on the importance of physical activity in CVD risk reduction. All agree on a minimum of 150 minutes per week of at least moderate activity.

There is also general consensus that if vigorous activity is undertaken then the amount required is less (NVDP only mentions suggestions for moderate activity). They recommend 75 minutes of vigorous physical activity (half of the moderate requirement). Many of the guidelines also recommend that the physical activity take place in bouts of 10 minutes or more. (ESC, ACC/AHA, CDC/AHA and JBS3). The general recommendation is to spread the activity over the course of the week. The 2 UK based guidelines (NICE and JBS3) and the CDC/AHA also mention that twice per week the activity should be of the form that also provides muscle strengthening. The 2 UK based guidelines also recommend referral to programmes where support or supervision is provided for those that may need support to change their lifestyle; this is particularly stated for people who are considered to be at high risk of developing CVD. The JBS3 also recommends community-based exercise initiatives for high-risk patients.

Blood pressure lowering

Lifestyle factors mentioned in guidelines specifically for lowering of BP include weight control, increased physical activity, moderation of alcohol, sodium restriction, increased consumption of fruit and vegetables and low fat dairy products (ESC, ACC/AHA, CDC/AHA and JBS3). The ACC/AHA guideline also mentions dietary patterns such as the DASH diet, the United States Department for Agriculture food pattern or the AHA diet.

Areas of disagreement

Cholesterol lowering

The recommendations for the lowering of cholesterol through lifestyle factors is recommended in most of the guidelines although most are not explicit as to which specific factors should be addressed beyond the general advice mentioned above. The ESC is one of the only guidelines that mention that the use of plant stenols and sterols can lower LDL cholesterol. The NICE guideline on the other hand very clearly recommends against plant stenols or sterols for primary or secondary prevention of CVD.

Meats

The recommendations regarding the consumption of meat products are variable. There is a general recommendation for predominantly consuming white meat, such as poultry. Two of the guidelines specifically emphasise poultry consumption (NVDP and ACC/AHA) and lean meat (NVDP). The JBS3 specifically mentions the avoidance of processed meats that tend to be high in trans-fatty acids.

Alcohol intake

There is a general consensus on limiting the intake of alcohol. However, the limits that are set are variable compared to other recommendations. Only the ACC/AHA guideline does not mention any recommendation on alcohol intake as they stipulate it is outside the remit of the specific clinical questions addressed in the guideline. The CDC/AHA guideline for women only, recommends < 7 servings (1 serving is 4 oz. of wine). The ESC also recommends a similar amount for women and 14 units for men per week. The UK guidelines have a higher upper limit. The JBS3 recommends <21 units for men and < 14 units per week for women. The NICE guideline makes a more generalised recommendation of not regularly drinking more than 3-4 units per day for men (i.e. no more than 21-28 units /week) and not regularly drinking more than 2-3 units per day for women (i.e. not more than 14 to 21 units per week).

Dietary patterns

The 2 dietary patterns that have most often been mentioned in the guidelines include the Mediterranean (ESC, NVDP, JBS3) and the DASH (ESC, ACC/AHA, CDC/AHA and JBS3) diets. The NICE guidance opted to avoid using the term Mediterranean diet in its recommendations as they felt the description was non-specific and they instead opted to recommend some of the components of what would be considered beneficial from a 'Mediterranean diet' instead.

Discussion

I identified 6 guidelines that make recommendations on lifestyle factors for total cardiovascular risk reduction in a primary prevention setting. There is a general consensus between the 6 guidelines about the importance of lifestyle in CVD risk reduction and it forms the cornerstone of almost all of the guidelines considered. This is regardless of whether pharmacotherapy is indicated or already being taken. There is agreement that this is useful in both primary and secondary prevention of CVD.

The recommendation on the need for adequate physical activity levels, smoking cessation, limiting intake of saturated fat and particularly avoiding trans fats, having a diet that is rich in fruit and vegetables, that includes fish and wholegrain and limiting salt intake are very similar between the guidelines. There is also a consensus on the recommendations to reduce intake of sugars with specific mention of sugar-sweetened beverages. This is particularly topical with the UK government's introduction of the 'sugar tax' and this being preceded in other countries such as Brazil with the goal of tackling obesity and diabetes.

There are differences noted in the recommendations for what is considered acceptable alcohol intake, regarding intake of meat products in general rather than specifically those that constitute saturated fats and trans-fats. There is a general trend to recommending poultry over red meat although this is not present in all guidelines. These differences suggest that the evidence base for these factors are not as solidified and may be areas that require further research for clarification.

There is no agreement on recommendation of specific dietary patterns, but the two most commonly mentioned include the Mediterranean and the DASH diets, which advocate specific macronutrients or whole foods rather than concentrating on micronutrients. It is interesting that the NICE guideline avoids using the term Mediterranean diet in their recommendations based on quality of the evidence and potential ambiguity with the term. The Mediterranean diet is comprised of abundant fruit, vegetables, cereals, beans, nuts and seeds, with olive oil, a low consumption of red meat and low to moderate consumption of dairy products and

wine. The Prevención con Dieta Mediterránea RCT tested the potential for such a diet to reduce CVD events in patients at elevated CVD risk. The multivariable adjusted HRs were 0.70 (95% CI 0.54 to 0.92) and 0.72 (95% CI 0.54 to 0.96) for groups assigned to a Mediterranean diet with extra- virgin olive oil and a group assigned to a Mediterranean diet with nuts, respectively, versus a control group consisting of a low fat diet [52]. The DASH study demonstrated that a diet rich in fruit, vegetables, and low fat dairy products reduced levels of total and saturated fat and lowered BP [226].

It should be borne in mind that individuals may have difficulties changing their lifestyle and behaviour, which is often based on long-standing behavioural patterns. These are usually framed during early years of life by an interaction of genetic and environmental factors. These factors may impede the ability to adopt a healthier lifestyle. In addition, changing advice from medical professionals over time also causes confusion and sometimes mistrust from the public. Awareness of these factors may facilitate empathy and by providing simple and practical advice this may support behavioural change.

Relative risk

It is recognised that in younger patients there may be an underestimation of future risk if only a 10-year period is considered rather than over a longer period. Thus lifetime or relative risk scores have been advocated in order to identify individuals who may be at high risk in the longer-term to encourage earlier recognition and implementation of lifestyle intervention, even if pharmacotherapy is not deemed necessary at that stage.

Relatively young people are at low absolute risk of a CVD event in the ensuing 10 years despite having many risk factors. For example, a man of 45 who smokes, has a systolic BP of 180 mmHg, and a blood cholesterol of 8 mmol/L has a risk of fatal CVD of only 4% over 10 years (SCORE charts), suggesting no need for drug treatment. However, the relative risk chart indicates that his risk is already 12-fold higher than that of a man with no risk factors [153]. In these groups it is increasingly recognised that lifestyle intervention should be emphasised earlier.

Conclusions

The importance of lifestyle interventions in the primary prevention of CVD is very clear. There is a general consensus on many lifestyle factors and their recommended amounts in the guidelines assessed and these should be included as an integral part of risk reduction programmes.

Chapter 7 - Personalised electronic coaching for primary prevention in high-risk individuals: A randomised controlled clinical trial - The Heart Attack Prevention Programme for You (HAPPY) London study

Preamble

This chapter includes the outcomes of the main research question of the HAPPY London study. I compare the change in primary and secondary outcomes to determine if e-coaching is more effective than SOC alone. The results of this chapter will guide whether a HAPPY London type programme should be more widely offered to those with elevated CVD risk.

Abstract

Background: CVD remains one of the leading causes of mortality globally. Innovative techniques are required to tackle the anticipated rise in CVD due to rising obesity, diabetes and an ageing population.

Personalised e-coaching using the Internet and emails may help motivate healthier living and be of clinical benefit in complementing current programmes for cardiovascular risk reduction.

Objective: To investigate whether personalised e-coaching (consisting of access to a personalised website and email prompts) on top of SOC is more clinically effective than SOC alone in reducing cardiovascular risk in asymptomatic individuals with high 10-year cardiovascular risk.

Methods: A 2-arm RCT (HAPPY London) was conducted from July 2013 to May 2015. Participants were adults with a high 10-year cardiovascular risk based on the UK validated QRISK2 score (QRISK2 ≥10%) and free of manifest CVD. Randomisation was stratified based on QRISK2 score (<20% or ≥ 20%) and allocation was 1:1 to e-coaching and SOC vs. SOC alone.

Primary end point was the change in PWV over 6 months. Secondary end points included change in cardiovascular risk scores, quality of life, physical activity levels, BP and CIMT.

Results: A total of 402 participants with mean age 65.5 (SD 5.6) years (62% males) were randomised; 205 (78, 38% women) were allocated to the intervention group and 197 (71, 36% women) were included in the control group. Primary outcome data were available for 194 (95%) of the intervention group and 184 (93%) of the control group.
After 6 months there was no difference in the reductions in PWV (mean difference between groups 0.10 m/s, 95 % CI (CI) -0.19 to 0.40, p =0.42). Modest, statistically significant improvements were seen in other CVD risk factors in both groups including BP, weight, total cholesterol, physical activity levels, Framingham and QRISK2 scores.

Conclusion: Personalised e-coaching did not show clinical effectiveness in CVD risk reduction when combined with SOC in a high-risk primary prevention cohort.

Background

CVD remains one of the leading causes of mortality worldwide accounting for about one-third of deaths [1]. Although CVD mortality rates have decreased, the rise in obesity, diabetes and an aging population in both Western countries and globally raises concern. National and international bodies have highlighted primary prevention of CVD, through risk factor reduction, as a potential solution to reduce the burden of CVD [2]. The magnitude of this health care crisis calls for innovative measures to improve cardiovascular health. There is some evidence that behaviour change using computer tailoring can be effective in changing lifestyle and risk factors [6,7]. Internet and email use has seen increased global uptake and these platforms hold potential in aiding preventative strategies, allowing efficient, easy to use and cost effective ways to improve the health and wellbeing of many. It may allow a way to maintain frequent contact between healthcare workers and patients, without overburdening existing healthcare facilities and facilitate patient involvement with increase motivation to manage personal health. The aim of e-coaching is to help encourage individuals to improve suboptimal factors lead a healthier lifestyle by identifying needs, setting goals, using strategies to support change and reinforcement through encouragement during the process [6]. The use of e-coaching has been applied to single risk factor modification such as dietary behaviour change [66], lipid lowering [74], increasing physical activity [68] and smoking cessation [77].

Guidelines on primary prevention now advocate using risk calculators to identify individuals at high-risk of developing future CVD events to facilitate risk reduction [30,31,153,17]. The QRISK2 calculator is validated for risk prediction in the UK population and is widely used in primary care [16,44].

Primary prevention studies generally require long follow-up and large participant numbers to powerfully detect hard cardiac end points. This creates obvious resource and administrative challenges. Use of robust surrogate markers can help identify potentially useful interventions that can then be further studied. I therefore used PWV which is the most validated method to non-invasively measure arterial stiffness and is recognised as a surrogate marker for future

cardiovascular events [227]. It is considered the gold standard index of aortic stiffness, as it is a relatively simple method with reported accuracy, reproducibility and an independent and strong predictor of adverse outcomes [104,105].

HAPPY initially used a method with generic lifestyle e-coaching as assessed in a study using a Dutch population (n=1000) over 3 months [83]. 141 of the participants with an intermediate to high cardiovascular risk were followed over 12 months. There was a relative reduction in cardiovascular risk of 13.8% using the PROCAM risk score. This study was however non-randomised and not controlled.

The primary objective of this study was to assess the clinical effectiveness of personalised, continuous e-coaching to support a healthier lifestyle as a primary prevention tool in reducing future cardiovascular risk in asymptomatic individuals with high predicted 10-year CVD risk.

My primary hypothesis was that computer-tailored e-coaching in addition to SOC would lead to greater reductions in the surrogate marker of aortic PWV compared to SOC alone. Our secondary hypothesis was that computer-tailored e-coaching in addition to SOC would lead to greater reduction in the QRISK2, BP, biomarkers of cardiovascular risk, CIMT and an improvement in quality of life compared to SOC alone.

Methods

See methods section for detailed information. In brief this was a single-centre, 2-arm RCT (ClinicalTrials.gov: NCT01911910). From June 2013 to November 2014, 402 adults with a high 10-year CVD risk score (QRISK2 score ≥ 10%) were recruited. Eligible patients were aged between 40 to 74 years, had no previous history of overt CVD, had easy access to the Internet and sufficient fluency in the English language to understand the personalised online content.

Recruitment was mainly conducted through postal invitation for potentially eligible individuals identified by primary care database searches. I also advertised through posters inside London buses, email invitations to university and hospital

staff and word of mouth. All interested individuals had to register on the study website (www.happylondon.info) and complete a brief online 'mini-check' screening questionnaire to check for eligibility. Potentially eligible individuals who had an estimated 10-year cardiovascular risk score of above 10% were invited to book an appointment, using the online calendar, to attend a screening visit at the research centre. Confirmation emails were sent with the appointment details and included the PIS sheet and a copy of the consent form.

Eligibility was confirmed after the first visit, once blood results were available to calculate the current QRISK2 score. Randomisation occurred prior to the second visit. Participants with a QRISK2 ≥ 10% were randomly assigned 1:1 to e-coaching with SOC or SOC alone, stratified according to either "moderate" (QRISK2 between 10 and 20%) or "high" risk (QRISK2 > 20%). Three subsequent predefined visits took place over 6 months; within 2 weeks of screening visit (baseline), 3 months and 6 months from baseline. Email appointment reminders were sent to participants 2 weeks and also 2 days prior to their visit. Assessment was performed using a variety of measures through lifestyle and quality of life questionnaires (EQ-5D-3L, SF-36, RPAQ and the 'big-five' personality traits questionnaire (from Professor Thomas Dohmen), BP checks (Omron 705IT, Omron Corporation, Kyoto, Japan), blood tests (following an 8-hour fast, for lipid profile, glucose, hsCRP and eGFR), ultrasound scans (Panasonic CardioHealth System, Panasonic Healthcare Co. Ltd, Yokohama, Japan) oscillometric method to assess PWV and pulse wave analysis (Vicorder device, Skidmore Medical, UK). A subgroup of the study population (50 from each randomised group, totalling 100 participants; with 96 actually having a scan) also underwent baseline and follow up CMR multi-parametric scanning. All non-CMR visits were performed at the research centre. All CMR visits were performed at dedicated 1.5 Tesla CMR (Philips, Best, Netherlands) scanning suites of Barts Health NHS Trust. The results from this sub-study will be presented in chapter 8.

Randomisation

Refer to chapter 3 for methods

Blinding

Outcome assessors were blinded to intervention arm when analysing the CMR and PWV data. Researchers and participants could not be blinded to the intervention during the study.

Intervention

In brief, the HAPPY London web-based tool provided each e-coaching group participant with a personalised score for their lifestyle and 10-year CVD risk score and provided tailored advice and information to improve suboptimal factors (Figure 50).

Personalised email reminders and tips for lifestyle improvement were sent (Figure 50). Participants with more suboptimal factors received more personalised tips. Bi-weekly health and lifestyle motivational news items with general advice were posted on the website for all participants to view to encourage healthier behaviour. Links to social networks, such as Facebook posting and the ability to allow chosen 'buddies' from family or friends to view their progress was encouraged to further motivate healthy behaviour. Refer to chapter 4 for detailed information about how the website development and functioning. See Intervention section of the methods in Chapter 3 for more details.

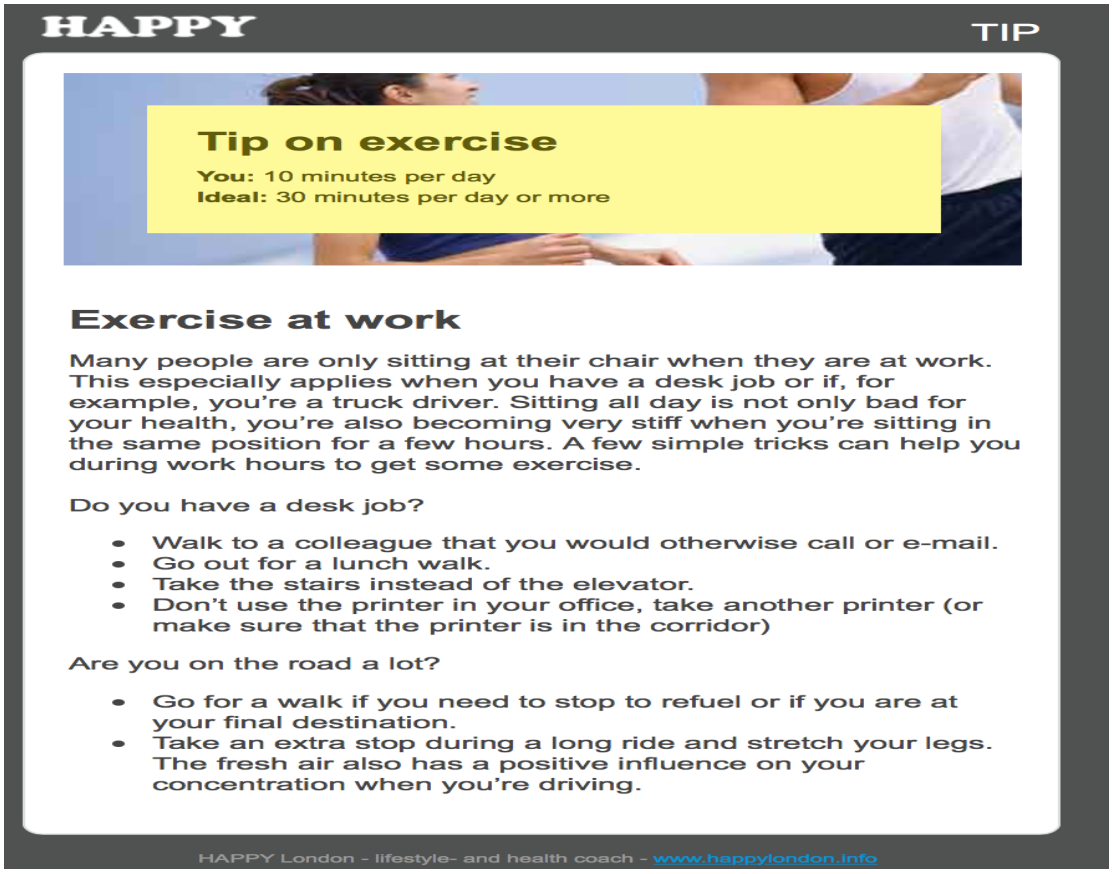


Figure 50. Example of tailored tip for participants that perform suboptimal physical activity

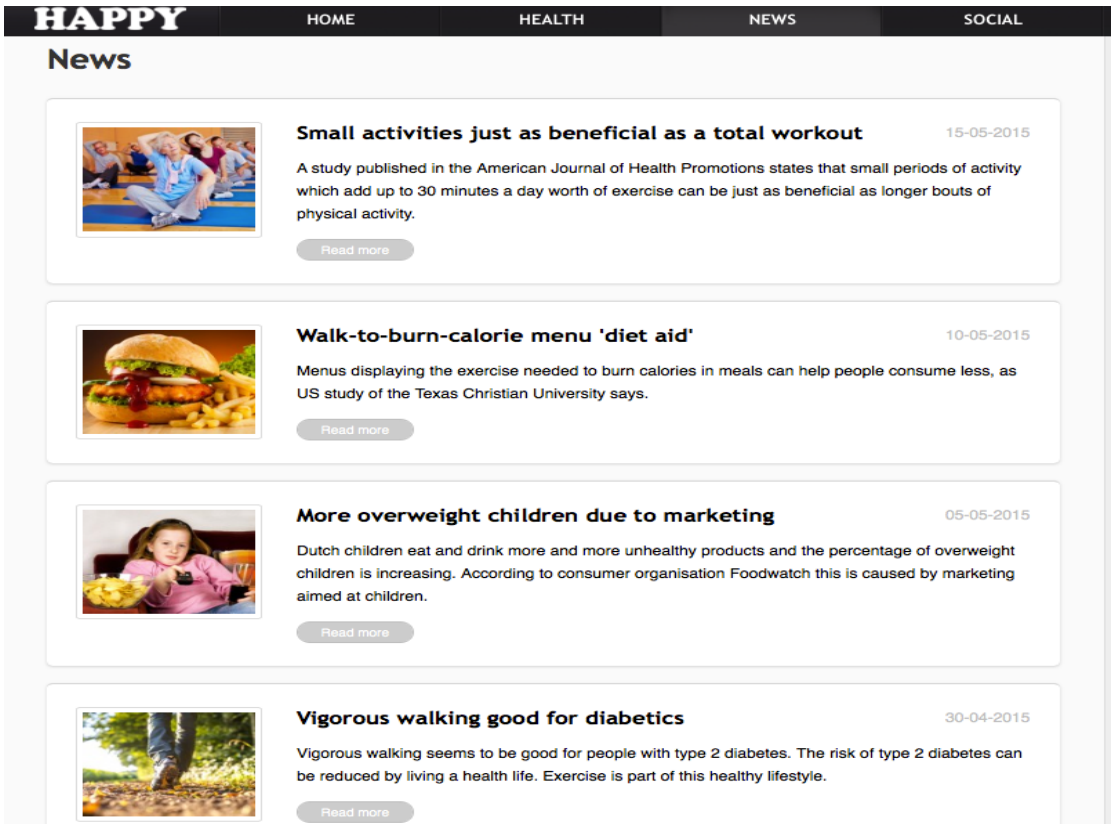


Figure 51. Example of general new item as seen on the HAPPY London website.

Standard of care

E-coaching and SOC group participant received personalised face-to-face counselling on suboptimal lifestyle and cardiovascular risk factors based on guideline recommendations during the second visit, lasting about 10-15 minutes[225]. All participants initially completed a lifestyle questionnaire, adapted from the original HAPPY study, to identify suboptimal factors. Tailored advice on factors including BP, cholesterol, glucose readings, smoking, weight, physical activity, fruit and vegetable intake, alcohol intake and stress was provided by me, a trained physician who was not blinded to the participants' intervention group.

Outcomes

Our primary outcome was the change in PWV from baseline to 6 months in the two treatment groups. Secondary outcomes included change in CIMT, quality of life (EQ-5D-3L and SF-36), LV mass by CMR, Framingham risk score, QRISK2 scores, self-reported RPAQ questionnaire, BP, alcohol intake, weight, BMI, cholesterol, glucose and high sensitivity c-reactive protein from baseline to 6 months. At the 6-month visit I documented any changes in medication occurring during the trial period. Specifically enquiring about initiation of statin therapy or blood pressure medication.

Procedures

Cardiovascular risk calculation

QRISK2 was calculated once visit blood results were available at visit baseline, 3-months and 6-months. However, due to changes in the QRISK2 algorithm during the study period I performed calculations for all visits again at the end of the study using the most up-to-date QRISK2 algorithm to standardise all the scores.

Pulse Wave Velocity

The Vicorder device was used to measure carotid femoral PWV and AI as markers of global arterial stiffness. Primary outcome was the change in PWV between 6

months and baseline. For more details see Chapter 3, under the 'pulse wave velocity' subheading of the Methods.

Statistical analysis

Analysis was performed on an intention to treat basis. Mean±SD was used for normally distributed variables. Median and interquartile ranges were used for data that are not normally distributed. T-test was used for normally distributed continuous measures and Chi2 for categorical variables. Where variables were not normally distributed non-parametric tests were used (Mann-Whitney for continuous and Wilcox rank sum test for categorical variables). Changes in PWV and other parameters between the treatment and control arms over 6 months were compared for statistical difference. Agreement between repeated analysed with a student's paired t-test with further analysis performed using Bland-Altman Plots. One extreme outlier (27 m/s) was found CFPWV output and was excluded from the analysis. The subsequent visit was also grossly different suggesting there was likely a measurement error.

Proposed sample size

See methods chapter 3

Results

Patients were recruited between June 2013 and November 2014, with all follow-up completed by May 2015. Of the 900 people who completed the online 'mini-check' for eligibility, a total of 491 fulfilled the preliminary inclusion criteria and accepted the invitation for participation, of these 402 were randomised as were confirmed to have a QRISK2 of 10% or more (Figure 52). The mean age was 65.5 ±5.6 years and the majority (63%) were males. Median 10-year QRISK2 score was 16.5% and mean Framingham Risk score was 17.5%. Demographics and baseline characteristics including CVD risk factors are included in Table 13. The proportion of participants with a high QRISK2 score was similar in both the e-coaching and SOC groups (36% vs. 31%, p= 0.33 as was the proportions of those at moderate

risk (64% vs. 69%, p= 0.33). Baseline measures were generally similar in both groups with no statistical difference except in the case of CFPWV (e-coaching 8.5 ±1.6, SOC 8.8 ±1.5, p= 0.027) and mean of the combined CIMT from the left and right carotids (e-coaching 0.705 ±0.13, SOC 0.736 ±0.13, p=0.02).

The major reason for not being randomised into the study was having a 10-year QRISK2 score of less than 10%. During the study 24 participants (6%) dropped out and did not have a follow up measurement (11 from e-coaching group and 13 from the SOC).

After 6 months there was no difference in the primary outcome measure of change in PWV between the intervention group and SOC (mean difference between groups 0.10 m/s, 95 % CI (CI) -0.19 to 0.40, p =0.42) with a similar reduction in the PWV in both the e-coaching and SOC groups (-0.156m/s vs. -0.260 m/s). Table 14 summarises the changes seen at follow up in each group and highlights the mean difference between groups.

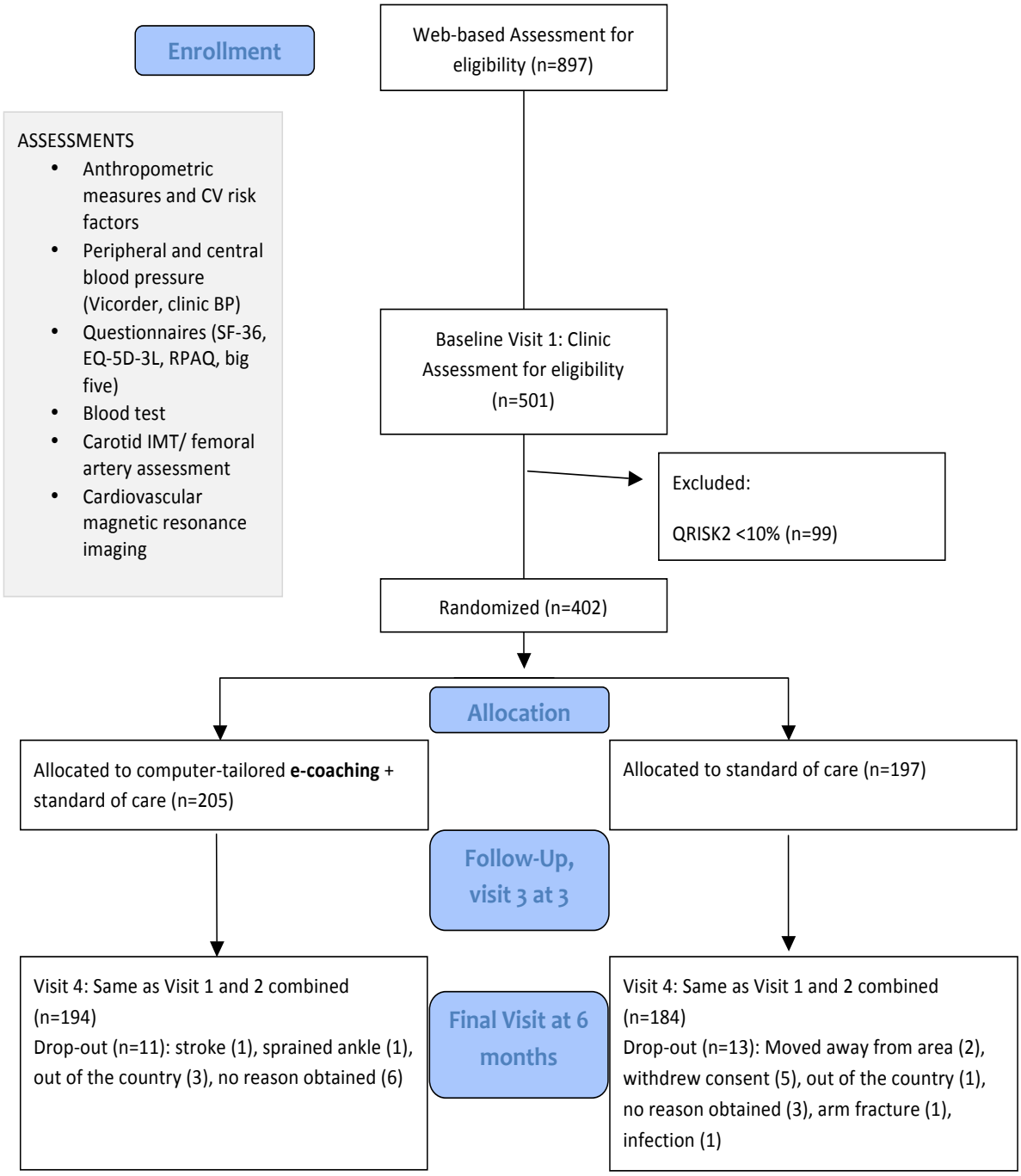


Figure 52. CONSORT flow diagram for the HAPPY London Study

Table 13. Demographics and baseline clinical characteristics for both groups

Demographics and baseline measures	E-coaching group (n=205)	SOC group (n=197)	P value
Age (years) mean(SD)	65.1 (6.3)	65.9 (4.8)	0.15
Demographics	**n (%)**	**n (%)**	
Male sex (%)	127 (62.0)	126 (64.0)	0.75
Smoking history			
Non-smoker	104 (50.7)	80 (40.6)	0.053
Ex-smoker	86 (42.0)	101 (51.3)	0.076
Light (<10)	9 (4.4)	9 (4.6)	1
Moderate (11-19)	6 (2.9)	3 (1.5)	0.53
Heavy (>20)	0	4 (2.0)	0.12
Ethnicity			
White	182 (88.8)	172 (87.3)	0.76
Indian	9 (4.4)	8 (4.1)	White
Pakistani	6 (2.9)	3 (1.5)	vs.
Bangladeshi	0	2 (1.0)	Non-white
Other Asian	3 (1.5)	0	-
Black Caribbean	1 (0.5)	3 (1.5)	-
Black African	0 (0)	2 (1.0)	-
Chinese	2 (1.0)	1 (0.5)	-
Other	2 (1.0)	6 (3.0)	-
Medical History			
Rheumatoid Arthritis	8 (3.9)	3 (1.5)	0.25
BP medication	105(51.2)	83 (42.1)	0.08
Cholesterol medication	98(47.8)	84(42.6)	0.40
Diabetes	35 (17.1)	22 (11.2)	0.12
Atrial fibrillation	9 (4.4)	11 (5.6)	0.75
Family History CAD	75(36.6)	60 (31)	0.25
Risk Scores			
QRISK2 (10-year risk, %) (median/IQR) all subjects	16.5 (12.7-23.1)	16.5 (12.6 – 21.1)	0.56 log
Framingham risk score (10-year risk, %) all subjects	16 (9)	17.8 (10)	0.54
Risk Stratification			
High risk (n)	73 (36)	62 (31)	0.38
QRISK2 for high risk (median/IQR)	25.7 (22.2 – 31.2)	26.3 (21.8 – 31.2)	0.99
Mod risk (n)	132 (64)	135(69)	0.38
QRISK2 for mod (median/IQR)	13.9 (11.8 – 16.2)	13.7 (11.6 – 16.7)	0.95
High risk or diabetes (n)	79 (39)	67 (34)	0.4
High risk or diabetes on statin (n)	56/79 (71%)	38/67 (57%)	0.07
Baseline Measures	**Mean (SD)**	**Mean (SD)**	
Systolic BP (mmHg)	132.5 (13.3)	132.3 (14.8)	0.88
Diastolic BP (mmHg)	79.2 (9.2)	80 (8.6)	0.34
Weight (Kg)	80.7 (18.4)	79.7 (16)	0.56

BMI (Kg/m2)	28.1 (5.6)	27.4 (4.4)	0.16
Hip circumference (cm)	104.7 (10.3)	103.6 (8.2)	0.25
Waist circumference (cm)	95.8 (15.2)	95.4 (12)	0.81
Total Cholesterol (mmol/L)	4.9 (1.1)	5.1 (1.1)	0.09
HDL (mmol/L)	1.6 (0.5)	1.6 (0.4)	0.95
LDL (mmol/L)	2.8 (1)	2.9 (1)	0.10
Triglyceride (mmol/L) median (IQR)	1.1 (0.8 – 1.5)	1.3 (0.8 – 1.5)	0.31
Glucose (mmol/L) median (IQR)	5.5 (5.1 – 6.0	5.5 (5.1 – 5.9)	0.71
hsCRP (mg/L) median (IQR)	1.2(0.7 – 2.5)	1.3 (0.7 – 2.4)	0.76
eGFR (mL/min/1.73sqm)	82.9 (20.1)	81.9 (17.9)	0.58
Physical activity (min pd)	70.8 (75.6)	64.9 (91.9)	0.48
Lifestyle score (out of 10, 10 being optimum score)	6.9 (1.3)	6.8 (1.3)	0.22
Surrogate Markers			
CFPWV corrected (m/s)	8.5 (1.6)	8.8 (1.5)	0.027*
CIMT (mean of right and left CIMT, mm)	0.705 (0.13)	0.736 (0.13)	0.02*
Quality of Life			
Self rated health state (best health 100) Median(IQR)	80 (65-90)	80 (65-90)	0.21
EQ-5D-3L VAS value (best QOL 1) Median(IQR)	0.76 (0.73 – 01.0)	0.76(0.69-1.0)	0.39
Carotid plaque present	185 (90%)	178 (90%)	0.73
Femoral plaque present	133 (65%)	133 (68%)	0.49

Abbreviations: BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CFPWV, carotid-femoral pulse wave velocity; CIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; EQ-5D-3L VAS, Euroqol, 5 dimension, 3 level visual analogue scale - validated questionnaire; HDL, high-density lipoprotein cholesterol; hsCRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol; Mod, moderate; pd, per day; QOL, quality of life

Table 14. Change in between intervention group and usual care group over the 6 months follow up

	E-coaching group		SOC			
	Follow-up	Mean change in 6 months	Follow-up	Mean change in 6 months	Mean difference between e-coaching and SOC over 6-months (95% CI)	p-value
	N=194	N=194	N=184	N=184		
Systolic BP (mmHg)	129.5 (13.6)	-3.183	130.7 (14.7)	-1.688	-1.5 (-4.2 to 1.2)	0.27
Diastolic BP (mmHg)	76.7 (9.1)	-2.371	78 (8.7)	-2.076	-0.29 (-1.6 to 1.1)	0.67
Weight (kg)	78.9 (18.1)	-1.216	79 (15.8)	-0.763	-0.45 (-1 to 0.1)	**0.10**
BMI (kg/m2)	27.4 (5.3)	-0.422	27.1 (4.4)	-0.247	-0.17 (-0.4 to 0)	**0.07**
Hip circumference (cm)	102.2 (9.9)	-2.188	101.8 (8.2)	-1.809	-0.38 (-1.2 to 0.5)	0.37
Waist circumference (cm)	92.7 (14.7)	-2.545	93.4 (12)	-2.048	-0.5 (-1.5 to 0.5)	0.31
Total Cholesterol (mmol/L)	4.8 (1)	-0.158	4.9 (1)	-0.197	0.04 (-0.1 to 0.2)	0.60
HDL (mmol/L)	1.6 (0.5)	-0.027	1.6 (0.4)	-0.017	-0.01 (-0.1 to 0)	0.64
LDL (mmol/L)	2.6 (0.9)	-0.102	2.8 (0.9)	-0.142	0.04 (-0.1 to 0.2)	0.56
Triglyceride (mmol/L)	1.2 (0.8)	-0.082	1.2 (0.6)	-0.113	0.03 (-0.1 to 0.1)	0.56
Glucose (mmol/L)	5.6 (1.3)	-0.293	5.5 (1.1)	-0.266	-0.03 (-0.2 to 0.2)	0.77
Creatinine	80.5 (17.1)	-0.433	80.9 (17.9)	-0.885	0.45 (-1.5 to 2.4)	0.64
HsCRP (mg/L)	2.3 (5.9)	-0.261	2.2 (5.4)	0.004	-0.27 (-1.9 to 1.3)	0.75
eGFR (mL/min/1.73 sqm)	82.3 (17)	-0.642	83 (20.2)	1.225	-1.87 (-4.8 to 1.1)	0.22
Alcohol per week (units)	7.9 (9.4)	-0.778	7.7 (8.2)	-1.081	0.3 (-0.7 to 1.3)	0.54
Physical activity (min pd)	98 (145.5)	25.102	74.2 (100.3)	8.448	16.65 (-10.3 to 43.6)	0.23
Lifestyle score	7.7 (1.2)	0.741	7.5 (1.3)	0.659	0.08 (-0.1 to 0.3)	0.45
CIMT (mean of left and right, mm)	0.72 (0.14)	0.014	0.75 (0.13)	0.015	0.02 (-0.017 to 0.015)	**0.91**
QRISK2 score	19.2 (8.5)	0.136	18.9 (8.6)	0.009	0.24 (-0.4 to 0.64)	0.63
Expected	19.6		19.3			

QRISK2 at 6 months*	(8.1)		(8.8)			
Framingham risk score (%over 10-years)	16.1 (8.9)	-1.232	16.6 (9.5)	-1.374	0.14 (-0.9 to 1.2)	0.79
PWV corrected#,	**8.3 (1.4)**	-0.156	**8.6 (1.8)**	-0.260	**0.10 (-0.19 to 0.40)**	**0.42**
Self-rated health state (best health 100) Median(IQR)	85 (75 – 90)	4.808	84 (68.5 – 90)	5.580	-0.77(-6.5 to 4.9)	0.79
EQ-5D-3L VAS value (best value 1) Median(IQR)	0.76 (0.70 – 1.0)	-0.000	0.76 (0.70 – 1.0)	0.01	-0.01 (-0.02 to 0.05	0.44
Statin initiated (n)	12		-		8	-
BP medication initiated (n)	4		-		4	-

Abbreviations: BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CIMT, carotid intima-media thickness; eGFR, estimated glomerular filtration rate; EQ-5D-3L VAS, Euroqol, 5 dimension, 3 level visual analogue scale - validated questionnaire; HDL, high-density lipoprotein cholesterol; hsCRP, high sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol; Mod, moderate; PWV, pulse wave velocity; QOL, quality of life

* Naturally expected due to older age only if other factors unchanged. QRISK increases with increasing age, # Corrected when extreme outlier excluded (a single reading of 27 m/s which was very different to a subsequent visit for the same patient and compared to all other readings)

There was also a similar modest improvement seen in both groups in a number of different cardiovascular risk factors although, again there was no difference between the e-coaching and SOC groups, respectively. These included improved systolic BP, diastolic BP, weight, hip circumference, waist circumference, fasting total cholesterol, fasting LDL cholesterol, fasting triglyceride, fasting glucose, and a reduction in the 10-year Framingham Risk score (-1.232 % vs. -1.374 %, p=0.79).

Lifestyle factor improvements were also seen to a similar extent in both groups including a reduction in alcohol units per week (-0.778 vs. -1.081, p=0.54), increased moderate physical activity, measured as minutes per week averaged over a 5-day week (25.102 vs. 8.448, p=0.54), and an improved overall lifestyle score which takes into consideration a number of lifestyle factors, with the best possible score of 10 (0.74 vs. 0.66, p=0.45).

With regards to quality of life measures, the self-rated health state scores, with 100 being the best health state, improved for both the e-coaching and the SOC groups over the 6-month period but with no difference between the two groups (4.81 vs. 5.58, 95% CI -0.65 to 4.9, p=0.79). The sum of the visual analogue scale value (which gives an indexed value based on the combination of the 5 dimensions of the EQ-5D-3L questionnaire) did not show any change over the study period either within or between the groups.

There was no reduction seen in CIMT measure over the 6-month period in either of the two groups. There was no difference between the two groups in the change over this period (0.014 vs. 0.015 mm, 95 CI of mean change -0.017 to 0.015, p=0.91).

Statin medication was initiated in 12 participants in the e-coaching group and 8 participants in the SOC following advise relayed to the GP. BP lowering medication was initiated in the 4 participants from the e-coaching group and 4 from the SOC group.

Table 15 summarises the number of participants that met accepted target ranges and shows a general improvement in the proportion achieving BP, BMI, total cholesterol, LDL cholesterol, fasting glucose readings, waist circumference targets and physical activity levels to a similar extent in both groups.

The reproducibility was good. The difference between repeated PWV measurements was –0.14 +/- 0.5 m/s (p = 0.38) with limits of agreement (LOA) of -1.10 to 0.82 m/s and intra class correlation coefficient was 0.89 (p <0.001, **Figure 53**).

Four participants were found to have what appeared to be significant atheroma on the carotid ultrasound. They were all referred to a vascular surgeon via their GP. Tow of the participants underwent carotid artery intervention and the other 2 were managed conservatively with further vascular clinic follow-up.

Table 15. Proportions achieving target levels

	E-coaching group		SOC group		Comparison between groups	
Risk factors/markers	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
	n=205	n=194	n=197	n=184	P value	P value
Systolic BP (<140mmHg)	156 (76)	158 (81)	142 (72)	142 (77)	0.36	0.31
Diastolic BP (<90 mmHg)	176 (86)	178 (92)	172 (87)	164 (89)	0.67	0.39
BMI (<25 kg/m2)	65 (32)	74 (38)	62 (31)	66 (36)	0.96	0.65
Total Cholesterol (<5 mmol/L)	110 (54)	116 (60)	95 (48)	101 (55)	0.30	0.37
LDL (<3 mmol/L)	118 (58)	121 (63)	104 (53)	108 (60)	0.34	0.51
Triglyceride (<1.7 mmol/L)	164 (80)	170 (88)	159 (81)	154 (84)	0.78	0.33
Glucose (<6.1 mmol/L)	162 (79)	162 (84)	155 (79)	149 (81)	0.99	0.60
Waist circumference*	117 (57)	127 (65)	120 (61)	119 (65)	0.44	0.87
Physical activity (>150 mins/ week)	131 (64)	109 (65)	111 (57)	104 (60)	0.15	0.36

Abbreviations: , BMI = Body mass index, BP = Blood pressure, E-coaching = Electronic coaching, LDL = low-density lipoprotein, SOC = Standard of care.
*<102cm males and <88cm females

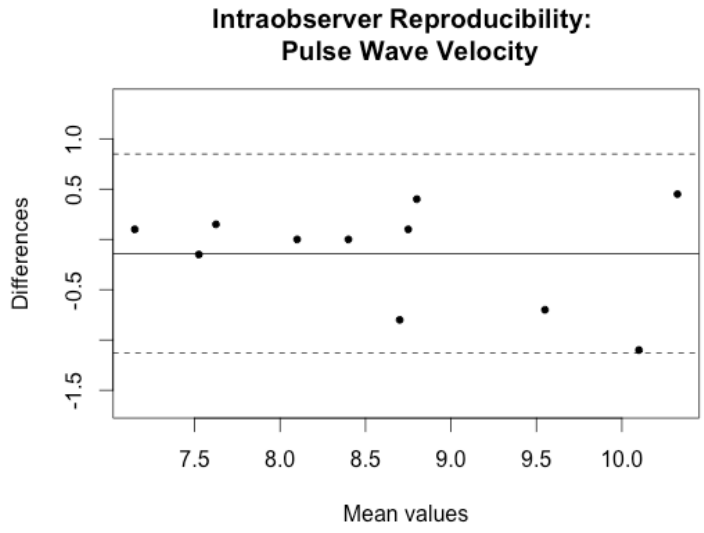


Figure 53. Bland Altman plot for intra observer reproducibility for PWV

Discussion

To my knowledge this is the first study to assess the impact of, personalised, e-coaching in a high risk primary prevention cohort using robust cardiovascular surrogate markers. This study showed that e-coaching, using Internet and email based heart attack prevention programme on top of the SOC compared with SOC alone did not reduce cardiovascular risk based on interval change of the PWV surrogate marker and other CVD risk markers. E-coaching and SOC both modestly improved PWV and a number of cardiovascular risk factors that translated in a reduced estimated 10-year CVD risk based on QRISK2 and Framingham scores.

The absence of improvement seen in the CIMT measurement may be accounted for by the modest overall improvements seen which may be too small to have led to a change. Six months may be too early to be able to have seen even a small reduction. CIMT is known to increase with age [157].

Impact of e-coaching in prevention

Computer based e-coaching uses the Internet and email that can be accessed from personal computers or more frequently now from mobile and remote devices. The potential benefits of using e-coaching include the flexibility of use when it is most convenient for the end user and being directly relevant to that individual when personalised. It can be time saving for the individual and for the healthcare system if it acts as a compliment to face-to-face visits by reducing need for frequent revisits thus potentially saving cost for the patients and the health system. It also has the potential for a wider reach with little additional cost after the initial setup process.

Challenges surround the use of e-coaching include the information governance process pertaining to maintaining robust internet security to ensure personal health information is transferred over a secure network. The absence or limiting of the 'human factor' replaced by an electronic device may limit the benefit. There is a

possibility of information overload especially if individuals have numerous suboptimal factors that they need to address and this may even become counter-productive. Long-term adherence to the behavioural programme may diminish and limit its effectiveness. Finally, without proven effectiveness it would be difficult to implement its widespread use due to the resources and cost associated with maintaining such a program. I did not formally undertake a cost – effectiveness analysis as planned as there was an absence of added effectiveness from with e-coaching over SOC. There is a financial cost from the implementation of an e-coaching programme and thus it would not currently be a cost-effective intervention.

The outcomes of e-coaching studies have been varied and the end points, designs and strategies utilised have been heterogeneous. In the area of secondary prevention, a Cochrane review by Devi et al. tried to determine the effectiveness of internet-based intervention targeting lifestyle change and medicines management in those with established CHD [228]. Eleven completed RCTs were identified targeting lifestyle management of CHD (7 trials) or physical activity promotion (4 studies). In general, the evidence was deemed to be of low quality due to lack of blinding, loss to follow-up and uncertainty around the effect size. Few studies measured clinical events or assessed health related quality of life.

Very few studies exist in the area of primary prevention and a meta-analysis assessing the effectiveness of internet-based interventions targeting participants with increased CVD risk identified 5 RCTs in diabetic patients and 4 in those with increased CVD risk predominantly due to high BP. The authors noted a shortage of studies investigating the effectiveness of internet-based interventions in improving direct CVD outcomes such as cardiac mortality or adverse events, which is an inherent challenge with primary prevention studies in relatively well individuals. They noted some evidence to suggest that interactive self-management programmes that include lifestyle education and self-monitoring of health behaviours may be of benefit in improving some clinical CVD risk factors such as BP [229]. However, most studies concentrated on patients with diabetics or those with hypertension.

A meta-analysis on computer tailoring found that it is unclear how elaborate a computer-tailored intervention should be to have an effect. It is not possible to relate the effects of the intervention to information given (the dose), because the interventions are usually not described in enough detail to make meaningful comparison possible [7].

The study included individuals who were deemed to have a high total cardiovascular risk. CVD risk assessment, using risk calculators to guide management is a concept that is now advocated in many primary prevention guidelines [17,30,31,153]. The study also utilised a number of robust and sensitive surrogate markers, which confirmed that risk reduction programmes have a modest improvement in future risk in general, but with no additional clinical benefit with the addition of e-coaching. Currently, primary care physicians provide face-to-face advice to those considered as having a high future cardiovascular risk profile. This is usually complemented with written booklet and information leaflets for the particular suboptimal factors that need addressing. Patients also utilise the Internet to search for advice and information on their condition or risk factors. Although, having a personalised webpage with all of this information in one place with blood test results and reminders may be expected to positively impact on ease of access to information and patient satisfaction, it does not, however, currently translate into a meaningful clinical benefit. It may still be argued that more information is better than less and may provide motivation for future change or at least better awareness of risk factors and health information. However, in most resource limited health care systems where there is an opportunity cost and other services with strong evidence base may potentially be denied funding as a consequence. This poses an ethical and resource allocation dilemma leading to rationalisation of intervention that does not show objective evidence of benefit. Evidence of effectiveness of a potentially costly health technology is vital before recommending its widespread use in resource limited health care systems.

Strengths and limitations

My study includes a variety of sensitive measures to evaluate outcomes including common contemporary cardiovascular risk markers including biomarkers,

physiological surrogate markers, imaging markers and questionnaires to assess lifestyle and quality of life. I included a large number of participants and this study forms one of the largest of its kind. Although not a blinded study I tried to avoid any sources of bias that may have effect study results. I had a very low drop-out rate of 6%, which may be partly reflective of the efficient online reminder systems for appointment and participant involvement with the study.

There were some limitations to the study. Participants and the researchers conducting the visits were not blinded. Although we were very strict in following the pre-specified protocol this may have led to possible bias. This does not appear to have had an impact on the final results. If we had more resources we would ideally have liked to include more blinding. Another limitation was that we did not include a third group of participants who could have just had baseline and follow-up assessment without any type of intervention (e-coaching or SOC) to better understand the natural variation in the population. However this may be an unrealistic strategy as those identified as being at high risk would normally receive some form of intervention either in the form of lifestyle advice or pharmacotherapy following assessment.

Anecdotally, the participants included in the study appears to included a large group of professionals and baseline characteristics such as physical activity appear to be better than population average and thus may represent a healthier group. This may reduce the impact seen from the programme. Volunteering effect may have been present and the cohort may have been healthier, of higher socioeconomic and educational level than the general population thus making generalisability challenging. Follow up was only for 6 months, if resources had allowed I would have extended the study period to a minimum of 1 year. The website was initially a Dutch initiative and some modifications were made to make it more relevant for the British population. However, certain aspects of the lifestyle questionnaires and website content may not have been culturally suited to the population. Ideally, I would have liked the full content of the programme to be tailored to the local cultural and language preferences. Only people with Internet access were eligible and may have created a selection bias. Guideline based intervention is not necessarily the SOC during most visits due to time constraints

and experience of some primary care staff (e.g. health care assistants and non-specialist nurses). An experienced cardiology research doctor performed interventions, whereas health check type programmes are commonly conducted by health care assistants or nurses and less frequently by a doctor. The majority of the subjects were Caucasians and thus it is difficult to generalise the findings to other ethnic groups due to differences in pathophysiology and cultural differences. Although we did try and target ethnic minorities the uptake was lower than expected which may partly be related to cultural acceptance of clinical trials or possibly language barriers in some cases.

Interpretation

Behavioural and risk factor counselling appears to have a modest improvement in risk but with no additional benefit seen when combined with e-coaching. Although the improvements in the individual factors are modest the combined effect of a number of factors may have an additive effect. If these improvements are maintained in the long term this may translate into prognostic benefit [230]. Further studies assessing the impact of smart phones and wearable mobile technology are required [65].

Conclusions

Personalised e-coaching did not show clinical effectiveness in CVD risk reduction when combined with current SOC in a high-risk primary prevention cohort. Implementing guideline recommendation that promote risk factor reduction for primary prevention can produce modest but significant improvements in a number of different cardiovascular risk factors in the medium term.

Chapter 8 – Impact of electronic coaching on cardiovascular risk reduction in a high-risk primary prevention population – A cardiovascular magnetic resonance sub-study

Preamble

This chapter includes the outcomes of the CMR sub-study. The main purpose of the CMR sub-study was to assess the changes that may be seen following predominantly lifestyle intervention over a 6-month follow-up period. This information can then be used to guide whether the use of CMR would be feasible and useful for future similar studies. The results could also be used to calculate sample sizes necessary for future studies to be sufficiently powered to show statistical difference.

Abstract

Background: Powering primary prevention clinical trials for hard clinical end points poses logistic and resource challenges. CMR imaging offers a range of powerful imaging parameters that can be used as outcome measures in clinical trials at reduced cost and follow-up duration and can inform performance of larger scale RCTs. Use of these surrogate markers in primary prevention with predominantly lifestyle interventions has been limited. Robust surrogate markers can help assess its clinical effectiveness and guide future widespread implementation.

Purpose: The primary aims of this sub-study were to 1. Assess for effect size of change in CMR surrogate markers with lifestyle changes over a short period of time (6 months). This would be useful for design of future larger phase 2 primary prevention trials with behavioural interventions, 2. To assess for determinants of these CMR surrogate marker changes and 3. To assess the feasibility and acceptability of CMR in a lifestyle intervention study.

Methods: This is a CMR sub-study of a single centre RCT. Between July 2013 and May 2015 I lead a single centre RCT of 402 participants, comparing e-coaching in addition to SOC vs. SOC alone. Estimated 10-year cardiovascular risk of 10% or more was required with no prior history of CVD. In this sub-study CMR scanning (Philips 1.5T), Vicorder device based CFPWV and cardiovascular risk assessment were performed at baseline and 6-month follow-up in the first 100 participants, with 1:1 allocation based on treatment arm. Surrogate markers of LV mass, aortic distensibility by CMR were assessed. I also performed oscillometric CFPWV and ultrasound derived CIMT measurements assessed against changes in cardiovascular risk factors from predominantly lifestyle interventions.

Results: Average age was 65.2 ± 5.8 years for the 86 participants that completed both baseline and follow-up CMR. Compared to baseline there was a non-significant reduction in LV mass in the whole group following predominantly lifestyle intervention (-1.68g, p=0.155). I did however see significant reduction in the distensibility of TAA (mean change -0.20 x 10^{-3} $mmHg^{-1}$, p=0.043), and TDA (mean change -1.61, p< 0.001). This appeared to be due to a combination of increase in the central pulse pressure and a reduction in the aortic strain. Both treatment groups showed reduction in LV mass (e-coach -2.01g vs. -1.27g, p= 0.74) and PWV (e-coach -0.30 m/s vs. -0.77 m/s, p= 0.08). Findings were consistent when LV mass was indexed to BSA. Weight and BMI improved more in the e-coaching group but Global risk scores, glucose and BP improved similarly with no statistical difference between the two groups. Some significant changes were seen between risk factor changes and surrogate marker changes over 6 months such as TAA distensibility and change in systolic BP, weight and glucose.

Conclusions: Multi-parametric CMR is feasible in primary prevention studies of lifestyle interventions. Further studies are needed before CMR and other surrogate markers can be accurately used in this setting. Personalised e-coaching did not show clinical effectiveness in risk reduction, except in the case of weight reduction, when combined with current SOC in this sub-study using known robust surrogate markers.

Background

Innovative techniques are required to tackle the anticipated rise in CVD due to rising obesity, diabetes and an ageing population. Personalised e-coaching using internet and email may help motivate healthier living[83]. Thus reducing the rising cardiovascular morbidity, which is known to be attributable largely to modifiable risk factors[4]. Powering primary prevention clinical trials for hard end points such as myocardial infarction and death, poses logistic and resource challenges. Surrogate markers may play an important role assessing outcomes particularly in this group of patients. CMR imaging offers a range of powerful imaging parameters to assess changes in cardiovascular structure and function, particularly in myocardial infarction studies [231-233]. These can be used as surrogate end points in clinical trials with high reproducibility and may reduce cost and follow-up duration, informing performance of larger scale RCTs.

The HAPPY London Study assessed the clinical effectiveness of offering e-coaching to complement SOC to a high-risk primary prevention cohort compared to SOC alone. I investigated the effect of predominantly lifestyle interventions on multiple pathophysiological cardiovascular pathways utilising non-invasive investigations. I used multi-parametric CMR imaging in a significant sub-group of patients from the HAPPY London Study along with other established non-invasive surrogate markers.

LV hypertrophy and aortic stiffness were the main CMR surrogate markers: The development of LV hypertrophy is a relatively early response to hypertension, demonstrable in children and adolescents with borderline elevations in BP [234]. LV hypertrophy is associated with increased cardiac mortality and morbidity [136]. LV mass index reduction with antihypertensive medications can be seen as early as 16 weeks, but most commonly LV mass index reductions (ranging from 4g/m2 to 22 g/m2) are assessed and reported after 10-12 months of treatment [173].

Aims

The primary aims were to 1) assess for effect size of CMR surrogate markers with lifestyle changes over a short period of time (6 months) which would be useful for design of future larger phase 2 primary prevention trials with behavioural interventions, 2) To assess for determinants of these CMR surrogate marker changes. The main CMR markers I wished to assess were changes in LV mass and aortic distensibility along with other non-invasive measures of aortic stiffness, in a high-risk, asymptomatic primary prevention cohort and 3) To assess the feasibility and acceptability of CMR in a lifestyle intervention study.

In a pre-defined secondary analysis, I wanted to see whether the type of intervention had an effect on change in CMR surrogate markers (but this had limited statistical power).

Methods

Between July 2013 and November 2015, 402 participants were recruited into a single centre RCT comparing e-coaching in addition to SOC vs. SOC alone with a 6 month follow-up. Estimated 10-year cardiovascular risk of 10% or more was required with no prior history of CVD.

In the sub-study of the HAPPY London clinical trial the first 100 participants (50 from each treatment arm with 1:1 allocation) from the total cohort of 402 were allocated a baseline and 6 month CMR scan (Philips 1.5T) along with the standard assessments of the HAPPY London study for these visits. See chapter 3 for more details.

Population

Men and women aged 40–74 with no history of clinical CVD. All participants were required to have access to the Internet and to have basic computer literacy in the English language. All participants had 10-year estimated CVD risk 10% or more, as

assessed by the QRISK2 score[44]. Participants were excluded if they had a previous diagnosis of myocardial infarction, stroke, transient ischaemic attack, or angina.

Consent and CMR safety check

The study was approved by the national ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki. During the first screening visit all participants gave written consent to take part in the study and also whether they were willing to undergo a CMR scan. A CMR safety checklist was completed at the first visit to assess for any contraindications and a blood test for renal function measurement was obtained to assess contraindication to contrast agents (eGFR <30 mL/min/1.73sqm).

Assessments and procedures

Please refer to Chapter 3 for further details on assessments and procedures carried out, including questionnaires, anthropomorphic variables, BP monitoring, Vicorder PWV and pulse wave analysis (CFPWV), CMR scanning and carotid artery ultrasound measurements.

CMR analysis

I performed the CMR analysis blinded to the intervention. Analysis was done on an intention-to-treat basis. Endocardial contours were manually segmented from the short-axis SSFP cine images and summed using semi-automated software (CVI 42, Circle Cardiovascular Imaging Inc., Canada), to quantify LV end diastolic, end systolic, stroke volumes and ejection fraction. LV epicardial contours were manually segmented at end diastole for calculating LV mass, based on the summation-of-discs method. Values were indexed to BSA. The papillary muscles were excluded from the LV mass measurement. LV mass was determined by the difference between endocardial and epicardial contours at end diastole (i.e. the sum of the myocardial area) times slice thickness plus image gap multiplied by the specific gravity of myocardium (1.05 g/mL). See Chapter 3 for more details on the CMR sequences and analysis and Figure 54 for a summary of the CMR protocol.

Statistical analysis

Statistical analysis was performed using R for Mac (Version 0.98.1102 – © 2009-2014 RStudio, Inc.). Descriptive and summary statistics are reported as mean and standard deviation for continuous variables and count and per cent for categorical variables. The distribution of the data was assessed visually. Continuous variables were expressed as mean ± SD for parametric variables and median with interquartile range for non-parametric variables. Differences in the total sub-study cohort, over the 6-month study period, were assessed using paired t-test. I used linear regression models to determine the treatment effects adjusted for the pre-specified covariates to assess relationship between change in risk factors and surrogate markers. Statistical significance was defined as a two-sided $p<0.05$. Patients were compared based on treatment arm of e-coaching vs. SOC. Differences between the group changes in the parameters between baseline and follow up scans were assessed using the independent t-test.

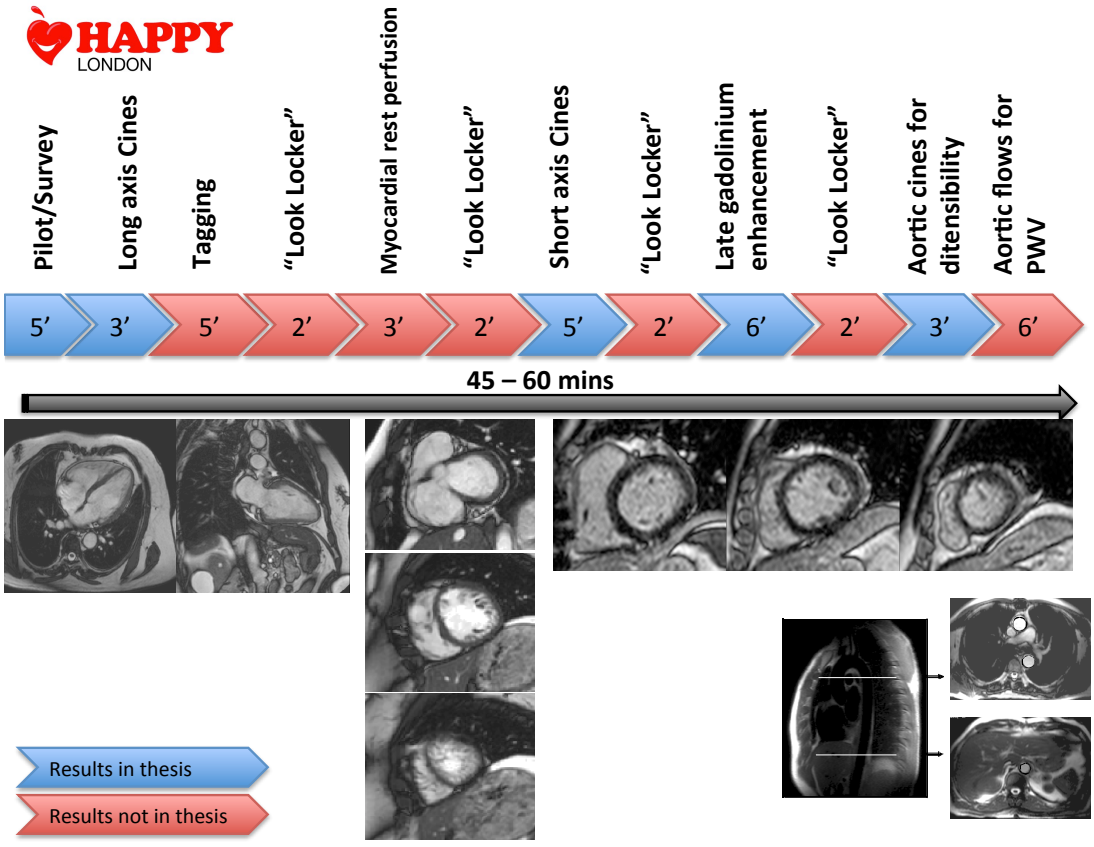


Figure 54. HAPPY London cardiovascular magnetic resonance scan protocol.

Results

50 of the first 57 e-coaching group and 50 of the first 56 SOC group consented to having a CMR scan and did not have a contraindication to scanning (Table 16). A total of 96 participants completed the CMR at baseline, 50 participants from the e-coaching group and 46 from the SOC. At follow-up 86 participants had an evaluable follow-up CMR scan.

Table 16. Participants scanned in the CMR sub-group

	E-coaching	**SOC**
Offered CMR	57	56
Accepted CMR and no contraindication	50	50
Attended	50	48 (2 failed to attend due to technical problem with booking system; no appointment received)
Scanned	50	46 (Claustrophobia = 1 Unable to fit in the scanner =1)
Follow-up scan	46 (Stroke =1 Unable fit scan into their schedule =1 Did not want repeat =1 Lost to follow up =1)	43 (Did not want repeat =2 Unable fit scan into their schedule =1)
Evaluable	44 (Technical difficulty retrieving from central server for analysis n=2)	42 (Technical difficulty retrieving from central server for analysis n=1)

Of those who did not have a baseline scan this was because the participants declined a scan despite no contraindication (n= 9), contraindications to contrast due to renal impairment (n=1) and contraindication due to metallic implants (n=3). Of those who attended, two of the participants from the SOC group did not have the scan due to claustrophobia (n=1) and being unable to fit in the scanner due to a large body habitus (n=1) and 2 other participants did not attend the CMR due to technical administrative problems with the online appointment system.

During the follow-up up phase, 7 participants did not have a repeat scan. This was due to not wanting a repeat scan (n=3), unable to attend due to work commitment (n=2), lost to follow-up (1), unable to attend due to stroke (n=1) and three other scans that were performed but unable to retrieve from central server due to technical issues at time of analysis (n=3).

2 of the participants were unable to have the scan out of the 96 at baseline. Suggesting that about 2% of subjects in similar studies may be unable tolerate or fit in the scanner on the day of the scan.

Mean age of all 86 participants who underwent both baseline and follow-up scan was 65.2± 5.8. See Table 17 for other demographics, baseline characteristics and measures. The majority were Caucasians (87%) and males (72%). Just over half of the group were on BP lowering (52%) or cholesterol lowering medication (57%) with a mean QRISK2 score of 19.1± 8.2.

Table 17. Demographics and baseline data for participants with baseline and follow-up CMR

Demographics and baseline measures	**Whole group (n=86)**
	Number (%)
Male sex	62(72)
Smoking history	
Non-smoker	37(43)
Ex-smoker	43(50)
Light (<10/day)	4(5)
Moderate (11-19/day)	0
Heavy (>20/day)	2(2)
Rheumatoid Arthritis	2(2)
BP medication	45(52)
Cholesterol medication	49(57)
Diabetes	**17(20)**
Atrial fibrillation	**4(5)**
Chronic kidney disease	**3(3)**
Caucasian	75(87)
	Mean± SD **Median (25-75%)**
Age, years	.
Systolic BP, mmHg	134.5± 13.9
Diastolic BP, mmHg	79.5± 9.5
Weight, kg	79.7± 14.6
BMI, kg/m²	27.3± 4.2
Body surface area, m²	1.9± 0.2
Hip circumference, cm	104.0± 7.1

Waist circumference, cm	96.0± 12.8
Total Cholesterol, mmol/L	4.7± 1.0
HDL, mmol/L	1.5± 0.4
LDL, mmol/L	**2.6**± 1.0
Triglyceride, mmol/L	1.3± 0.7
Glucose, mmol/L	6.0± 1.5
Creatinine	79.9± 15.3
HsCRP, mg/L	2.7 ±6.4
eGFR, mL/min/1.73sqm	85.0± 17.0
Fruit per day, potions	2.8± 1.6
Veg per day, g	208.1± 125.7
Alcohol per week, units	8.2 ± 10.5
Physical activity min/week (mean)	298.5±341
Stress score	6.3± 5.0
Lifestyle score, out of 10, 10 being optimum score	6.8± 1.3
QRISK2, 10-year risk, %	19.1± 8.2
Framingham risk score, 10-year risk, %	18.8± 9.1
Augmentation index, %	22.3± 7.4
CFPWV, m/s	**8.1**± 1.4
CIMT left, mm	0.707± 0.161
CIMT right, mm	0.706± 0.177
CMR parameters	
Heart rate, bpm	62.9±11.4
LV EDV, ml	150.4± 34.4
LV ESV, ml	53.1± 18.7
LV SV, ml	97.3± 22.0
LV EF, %	65.2± 7.0
LV myocardial mass, g	96.4± 25.0
LV EDV i, ml/m²	77.4± 13.9
LV ESV i, ml/m²	27.3± 8.6
LV SV i, ml/m²	50.1± 9.0
LV myocardial mass i, g/m²	49.4± 10.1
RV EDV, ml	174.0± 42.4
RV ESV, ml	79.8± 26.2
RV SV, ml	94.2± 21.7
RV EF, %	54.7± 6.4
RV EDV i, ml/m²	89.3± 16.8
RV ESV i, ml/m²	40.8± 11.1
RV SV I, ml/m²	48.5± 9.2

Abbreviations: BMI = Body mass index, BP = Blood pressure, CFPWV = Carotid-femoral pulse wave velocity, CIMT = Carotid intima media thickness, CMR = Cardiovascular magnetic resonance, EDV = End diastolic volume, EF = Ejection fraction eGFR = Estimated glomerular filtration rate, ESV = End systolic volume, HDL= High-density lipoprotein cholesterol, HsCRP = High sensitivity C-reactive protein, i = indexed (to body surface area), LDL = Low-density lipoprotein cholesterol, LV= Left ventricle, QRISK2 = UK validated cardiovascular risk prediction score, RV = Right Ventricle, SV = Stroke volume

Changes in the whole cohort

In the whole cohort (e-coaching and SOC combined) there were modest but statistically significant improvements in systolic BP (-2.2%), diastolic BP (-4.7%), weight (-1.85%), hip circumference (-4.2%), waist circumference (-3.4%), fasting glucose (-11.7%) and physical activity levels (61.8%, Table 18). Lifestyle questionnaire scores (10 being the best score) were better at follow up (14.7%) and there was a reduction in the stress levels based on the reduced stress scores (-17.5%). This translated in an overall significant reduction in the Framingham risk score (-6.4% of baseline) but the QRISK2 was similar at follow-up. PWV was significantly improved at follow-up with a 7.4% reduction.

Over the 6-month follow up period despite modest but significant reduction noted above and corresponding reduction in the risk estimation score there was no significant difference noted in the LV mass (baseline 96.0 g vs. 94.7 g at follow up, p=0.155). I did however see significant reduction in the distensibility at TAA (mean change -0.20 x 10^{-3} $mmHg^{-1}$, p=0.043) but not at TDA or ABA. However, this was in the opposite direction to what would be expected by the improvements seen in the lifestyle and other risk factors. This was partly driven by an increase in the central aortic pulse pressure at follow up (baseline 55.3 mmHg vs. 56.6 mmHg at follow-up, p=0.294) and a reduction in the TAA maximum aortic diameter and strain.

The CIMT measurements also showed a similar effect with an increase in CIMT at follow-up but a significant increase seen only in the left carotid measure (baseline 0.71mm vs. 0.73mm, p=0.038).

Table 18. Comparison of baseline and follow-up measures in those undergoing both CMR scans

	Baseline (n=86)	Follow-up (n=86)	p value	Mean Difference	95% CI	
Systolic BP, mmHg	134.5	131.5	0.024*	-2.99	-5.58	-0.40
Diastolic BP, mmHg	79.5	75.8	<0.001*	-3.70	-5.05	-2.34
Weight, kg	79.7	78.3	<0.001*	-1.37	-1.86	-0.87
BMI, kg/m²	27.3	26.8	<0.001*	-0.49	-0.67	-0.31
Hip circumference, cm	104.0	99.6	<0.001*	-4.41	-5.27	-3.54
Waist circumference, cm	96.0	92.7	<0.001*	-3.27	-4.59	-1.95
Total Cholesterol, mmol/L	4.7	4.7	0.53	-0.05	-0.20	0.10
HDL, mmol/L	1.5	1.5	0.199	0.02	-0.01	0.05
LDL, mmol/L	2.6	2.6	0.511	-0.04	-0.18	0.09
Triglyceride, mmol/L	1.3	1.2	0.346	-0.05	-0.14	0.05
Glucose, mmol/L	6.0	5.3	<0.001*	-0.66	-0.88	-0.45
Creatinine	79.9	80.6	0.447	0.66	-1.06	-2.39
HsCRP, mg/L	2.7	1.6	0.135	-1.07	-2.48	0.34
eGFR, mL/min/1.73sqm	85.0	83.9	0.217	-1.29	-3.36	0.77
Fruit per day, potions	2.8	3.0	0.045*	0.29	0.01	0.58
Veg per day, g	208.1	231.4	0.041*	21.73	0.95	42.52
Alcohol per week, units	8.2	8.2	0.414	-0.41	-1.39	0.58
Physical activity min/week (mean)	298.5	483	0.012*	35.56	7.89	63.23
Stress score	6.3	5.2	0.015*	-1.05	-1.89	-0.21
Lifestyle score, out of 10, 10 being optimum score	6.8	7.8	<0.001*	0.94	0.70	1.18
QRISK2, 10-year risk, %	19.1	19.2	0.931	0.02	-0.49	0.53
Framingham risk score, 10-year risk, %	18.8	17.6	0.022*	-1.29	-2.39	-0.19
AI, %	22.3	23.9	0.023*	1.70	0.24	3.15
CFPWV, m/s	8.1	7.5	<0.001*	-0.65	-0.91	-0.39
CIMT left, mm	0.71	0.73	0.038*	0.03	0.00	0.05
CIMT right, mm	0.71	0.72	0.250	0.01	-0.01	0.04

CIMT combined, mm	0.70	0.72	0.007*	0.02	0.01	0.04
Heart rate, bpm	62.9	60.7	0.031*	-2.15	-4.41	-0.20
BSA	1.90	1.85	0.095	-0.09	-0.19	0.02
LVEDV, ml	150.4	152.2	0.233	-1.80	-1.18	4.78
LVESV, ml	53.1	54.8	0.141	1.66	-0.56	3.88
LVSV, ml	97.3	97.4	0.917	0.14	-2.53	2.81
LVEF, %	65.2	64.5	0.292	-0.67	-1.92	0.59
LV myocardial mass, g	96.4	94.7	0.155	-1.68	-4.00	0.65
TAA area max, mm^2	961.2	953.3	0.010*	-16.24	-28.54	-3.94
TDA area max, mm^2	532.1	532.8	0.118	-5.36	-12.11	1.39
ABA area max, mm^2	483.1	485.2	0.175	-8.55	-20.98	3.88
TAA strain, %	0.11	0.10	0.013*	-0.01	-0.02	-0.00
TDA strain, %	0.11	0.12	0.521	0.00	-0.01	0.01
ABA strain, %	0.17	0.05	0.333	0.00	-0.00	0.01
TAA distensibility, 10^{-3} $mmHg^{-1}$	2.10	1.87	0.043*	-0.20	-0.40	-0.01
TDA distensibility, 10^{-3} $mmHg^{-1}$	3.8	2.1	<0.001*	-1.61	-2.01	-1.21
ABA distensibility, 10^{-3} $mmHg^{-1}$	3.21	3.23	<0.967	-0.00	-0.21	0.21
Central aortic pulse pressure, mmHg	55.3	56.6	0.294	1.22	-1.08	3.54

Paired t-test used.

Abbreviations: ABA = Abdominal aorta BMI = Body mass index, BP = Blood pressure, BSA = Body surface area, CFPWV = Carotid-femoral pulse wave velocity, CIMT = Carotid intima media thickness, CMR = Cardiovascular magnetic resonance, EDV = End diastolic volume, EF = Ejection fraction eGFR = Estimated glomerular filtration rate, ESV = End systolic volume, HDL= High-density lipoprotein cholesterol, HsCRP = High sensitivity C-reactive protein, i = indexed (to body surface area), LDL = Low-density lipoprotein cholesterol, LV= Left ventricle, QRISK2 = UK validated cardiovascular risk prediction score, RV = Right Ventricle, SV = Stroke volume, TAA = Thoracic ascending aorta, TDA = Thoracic descending aorta

Relationship of surrogate markers with changes in participant variables

Univariate regression analysis showed some significant relationship in changes seen in LV mass, PWV, combined CIMT (average of left and right CIMT) or thoracic aortic distensibility with changes in participant risk markers such as BP, weight and lipid profile and glucose (see Table 19 for full list). A significant relationship was noted between TAA distensibility with systolic BP change (β = -0.017, p=0.036), weight change (β =-0.124, p=0.003) and glucose change (β =0.202,

p=0.040). The impact of BP is likely related to the fact that aortic pulse pressure (derived from systolic and diastolic BP) is used to calculate distensibility. There was also a positive relationship of total cholesterol and the average of the combined left and right CIMT (β = 0.022, p=0.046) with a rise in cholesterol associated with a rise in CIMT.

Relationship between changes in surrogate markers

Changes in TAA strain and distensibility were the only factors predictive of a change in LV mass over the 6-month period (β=-84.939, p=0.002 and β=-4.622, p=0.001, respectively). Suggesting that a rise in LV mass is associated with a reduction in TAA strain and distensibility. A reduction in TDA distensibility was predictive of a rise in CFPWV (β = -0.156, p=0.009). CIMT changes were not associated with changes in other surrogate markers using univariate regression. Changes in TAA distensibility were associated with change in QRISK2 score (β= -0.048, p=0.025) and both TDA and ABA distensibility (β= 0.275, p=<0.001 and β=0.275, p=0.010).

Table 19. Regression analysis – Relationship of surrogate marker change with change in variables over time

Variable n=86	Left ventricular mass		CFPWV m/s		Average CIMT left and right, mm		Thoracic aorta distensibility , 10^{-3} $mmHg^{-1}$	
	Univariate		Univariate		Univariate		Univariate	
	β	P value	β	P value	β	P value	β	P value
Δ Systolic BP, mmHg	0.046	0.642	0.001	0.904	-0.001	0.321	-0.017	0.036*
Δ Diastolic BP, mmHg	0.279	0.134	0.008	0.643	-0.002	0.127	-0.024	0.123
Δ Weight, kg	-0.022	0.965	0.041	0.362	-0.002	0.526	-0.124	0.003*
Δ Hip circumference, cm	-0.142	0.630	-0.005	0.864	-0.002	0.370	-0.005	0.075
Δ Waist circumference, Δ cm	-0.288	0.133	-0.019	0.364	-0.000	0.837	-0.020	0.6224
Δ Total cholesterol, mmol/L	0.775	0.648	-0.114	0.443	0.022	0.046*	0.122	0.454
Δ Glucose, mmol/L	-1.442	0.222	-0.077	0.451	-0.004	0.677	0.202	0.040*
Δ HsCRP mg/L	-0.167	0.379	0.001	0.963	-0.000	0.921	-0.012	0.422
Δ Physical activity, mins over 5 days	0.012	0.243	0.001	0.517	-0.000	0.914	-0.001	0.280
Δ Lifestyle score (out of 10)	-2.014	0.127	-0.190	0.086	-0.000	0.992	0.220	0.054
Δ QRISK2 score, 10 year risk %	0.080	0.874	-0.044	0.334	0.003	0.448	-0.048	0.025*
Δ Framingham risk score, 10 year risk %	0.229	0.320	-0.027	0.181	0.003	0.087	-0.034	0.075
Δ Augmentation index	0.268	0.129	0.006	0.681	-0.000	0.847	0.016	0.301
Δ CFPWV, m/s	0.175	0.893	-	-	-0.001	0.952	0.169	0.133
Δ CIMT left, mm	-5.214	0.634	0.187	0.846	-	-	-0.007	0.994
Δ CIMT right, mm	2.627	0.808	-0.335	0.728	-	-	-0.193	0.834
Δ TAA strain, %	-84.939	0.002*	-2.748	0.248	-0.012	0.947	-	-

Δ TDA strain, %	50.808	0.134	-2.610	0.405	-0.143	0.529	1.907	0.502
Δ ABA strain, %	-13.407	0.661	-0.022	0.994	-0.203	0.317	-2.704	0.275
Δ TAA distensibility, 10^{-3} $mmHg^{-1}$	-4.622	0.001*	-0.181	0.133	-0.002	0.853	-	-
Δ TDA distensibility, 10^{-3} $mmHg^{-1}$	-0.215	0.761	-0.156	0.009*	-0.007	0.151	0.275	<0.001*
Δ ABA distensibility, 10^{-3} $mmHg^{-1}$	-1.943	0.149	-0.175	0.133	-0.008	0.344	0.275	0.010*

Abbreviations: ABA = Abdominal aorta, BMI = Body mass index, BP = Blood pressure, BSA = Body surface area, CFPWV = Carotid femoral pulse wave velocity, CIMT = Carotid intima media thickness, CMR = Cardiovascular magnetic resonance, EDV = End diastolic volume, EF = Ejection fraction, eGFR = Estimated glomerular filtration rate, ESV = End systolic volume, HsCRP = High sensitivity C-reactive protein, i = indexed (to body surface area), LV= Left ventricle, QRISK2 = UK validated cardiovascular risk prediction score, RV = Right Ventricle, SV = Stroke volume, TAA = Thoracic ascending aorta, TDA = Thoracic descending aorta

Changes between intervention groups over 6 months

In this sub-study cohort weight and BMI reduced significantly more in the e-coaching group (e-coach -2.02 kg vs. -0.68 kg in SOC, p=0.006 and -0.70 kg/m^2 vs. -0.27 kg/m^2) but without a significant difference seen in the LV mass (Figure 55). There were similar modest changes in the systolic BP, diastolic BP, hip circumference, waist circumference, fasting glucose, and alcohol intake in both groups, but with no significant difference between the interventions for changes in variables including surrogate markers (Table 20).

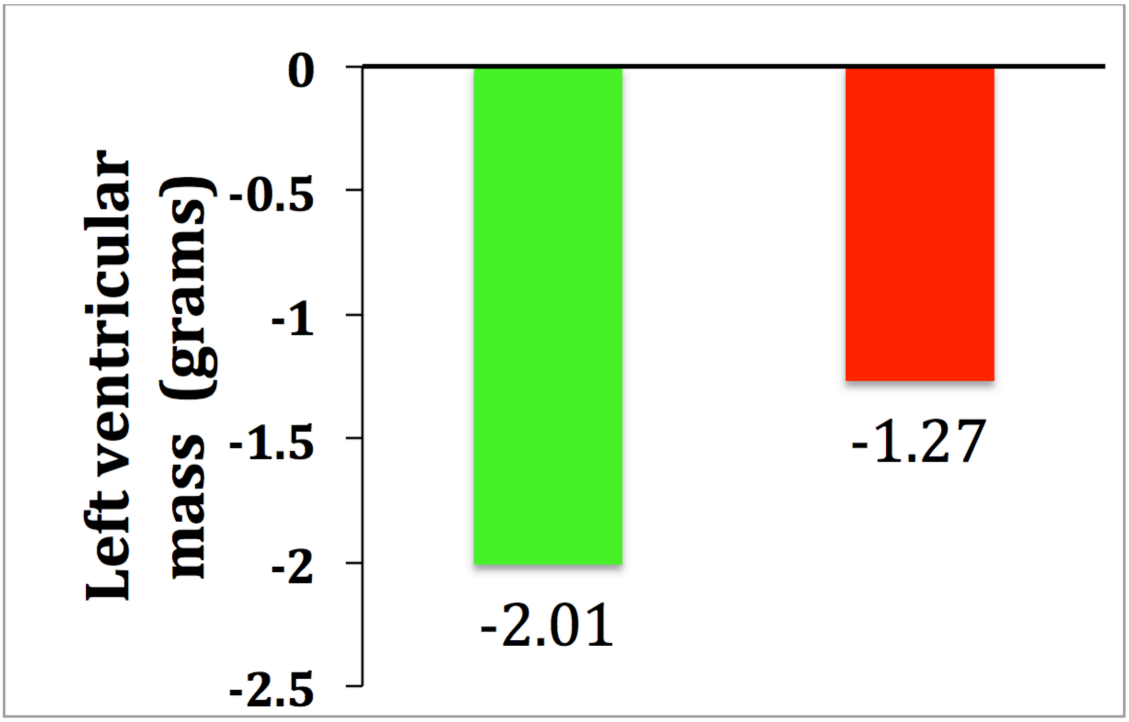


Figure 55. Change in LV mass in the e-coaching and SOC groups over 6 months (e-coach -2.01g vs. -1.27g, p= 0.738).

Table 20. Change in vascular risk factors and surrogate markers between e-coaching group and SOC over the 6 months follow up

	Change over 6 months			
Risk factors/markers	E-coach	SOC	Differences (95% CI)	p-value
	(n= 44)	(n= 42)		
Systolic BP, mmHg	-0.50	-5.60	-10.21 – 0.03	0.051
Diastolic BP, mmHg	-2.50	-4.96	-5.15 – 0.22	0.071
Weight, kg	**-2.02**	**-0.68**	**0.39 – 2.29**	**0.006***
BMI, kg/m²	**-0.70**	**-0.27**	**0.08 – 0.78**	**0.016***
Hip circumference, cm	-4.68	-4.11	-1.17 – 2.30	0.519
Waist circumference, cm	-3.99	-2.52	-1.18 – 4.13	0.273
Total Cholesterol, mmol/L	0.02	-0.12	-0.44 – 0.17	0.365
HDL, mmol/L	0.01	0.03	-0.03 – 0.08	0.404
LDL, mmol/L	0.03	-0.13	-0.44 – 0.11	0.242
Triglyceride, mmol/L	-0.04	-0.05	-0.21 – 0.17	0.850
Glucose, mmol/L	-0.68	-0.64	-0.38 – 0.47	0.831
Creatinine	0.07	1.43	-1.94 – 4.93	0.389
HsCRP, mg/L	-2.17	0.06	-0.57 – 5.01	0.116
eGFR, mL/min/1.73sqm	-0.26	-2.88	-7.23 – 0.96	0.132
Fruit per day, potions	0.34	0.24	-0.67 – 0.47	0.732
Veg per day, g	29.17	14.48	-56.38 – 26.97	0.484
Alcohol per week, units	-0.54	-0.27	-1.73 – 2.54	0.793
Physical activity min/5 days (mean)	25.31	45.55	-35.17 – 75.65	0.469
Stress score	-0.95	-1.15	-1.89 – 1.49	0.813
Lifestyle score, out of 10, 10 being optimum score	0.83	1.05	-0.26 – 0.71	0.361
QRISK2, 10-year risk, %	**0.33**	**-0.30**	**-1.64 – 0.39**	**0.223**
Framingham risk score, 10- year risk, %	-0.39	-2.24	-4.06 – 0.35	0.098
AI, %	1.60	1.79	-2.73 – 3.11	0.897
CFPWV, m/s	-0.47	-0.84	-0.90 – 0.16	0.171
CIMT left, mm	0.04	0.01	-0.08 – 0.01	0.139
CIMT right, mm	0.01	0.02	-0.04 – 0.05	0.786
Heart rate, bpm	-1.70	-2.62	-4.81 – 2.98	0.642
Body surface area, m²	-0.10	-0.07	-0.18 – 0.24	0.760
LVEDV, ml	2.11	1.48	-6.65 – 5.40	0.837
LVESV, ml	2.10	1.20	-5.35 – 3.55	0.688
LVSV, ml	0.01	0.28	-5.15 – 5.70	0.920

LVEF, %	-0.88	-0.45	-2.08 – 2.95	0.731
LV myocardial mass, g	-2.01	-1.27	-3.89 – 5.47	0.738
LVEDV i, ml/m²	0.21	-0.53	-5.99 – 4.50	0.779
LVESV i, ml/m²	0.42	0.23	-2.86- 2.47	0.887
LVSV i, ml/m²	-0.23	-0.79	-4.54 – 3.42	0.782
LV myocardial mass i, g/m²	-1.73	-1.42	-3.50 – 4.12	0.871
RVEDV, ml	1.50	8.09	-1.34 – 14.52	0.102
RVESV, ml	5.76	6.67	-5.72 – 7.55	0.785
RVSV, ml	-4.26	1.41	-0.01 – 11.36	0.050
RVEF, %	-3.03	-1.65	-1.24 – 4.00	0.298
RVEDV I, ml/m²	0.30	2.87	-3.89 – 9.03	0.431
RVESV I, ml/m²	2.55	2.88	-3.89 – 4.56	0.875
RVSV I, ml/m²	-2.27	-0.04	-1.66 – 6.12	0.257

Abbreviations: BMI = Body mass index, BP = Blood pressure, CFPWV = Carotid-femoral pulse wave velocity, CIMT = Carotid intima media thickness, CMR = Cardiovascular magnetic resonance, HsCRP = High sensitivity C-reactive protein, EDV = End diastolic volume, EF = Ejection fraction, eGFR = Estimated glomerular filtration rate, ESV = End systolic volume, HDL= High-density lipoprotein cholesterol, i = indexed (to body surface area), LDL = Low-density lipoprotein cholesterol, LV= Left ventricle, QRISK2 = UK validated cardiovascular risk prediction score, RV = Right Ventricle, SV = Stroke volume

Incidental findings

In this group with high estimated 10-year CVD risk I identified 3 participants (3%) with CMR evidence of previous myocardial infarctions that was not previously known. This is a lower percentage than previously published population observational studied [178]. One of the participants was diagnosed as being human immunodeficiency virus positive (but was stable on antiretroviral medications for many years) and had a coronary angiogram performed 10-year prior that was reported as normal. He had no obvious symptoms of previous cardiac chest pain. The other 2 had a subendocardial infarction affecting only 1 regional segment and the LV function remained in the normal range.

Renal masses that were identified were confirmed to be cysts on subsequent ultrasound (n=3, 3%). Hepatic cysts (n=2, 2%)) and moderate aortic regurgitation in one subject who was asymptomatic and one participant with a thyroid goitre. Only 1 CMR scan led to a low to intermediate suspicion of a lung mass, which was confirmed as a benign finding on subsequent targeted computed tomography of the chest.

Regards side effects 1 subject who was anxious at the time of the scan reported headache that settled after 1-2 days but he declined the follow up scan. 1 participant that had a BMI in the obese range and a large waist circumference complained of "body ache" for 1-2 days following the scan. He had the follow-up scan and tolerated it much better after losing 3-4 kg in weight.

Discussion

In the total CMR sub-study cohort I noted that there were modest but significant improvements in the cardiovascular measures including BP and weight. The effect of this was not seen in the LV mass. Peripheral measurements of BP showed an average reduction in the group, however there was a reduction in distensibility, which was unexpected suggesting that the arteries became stiffer. This was driven partly by an increase in central aortic pulse pressure and a small reduction in the aortic area and strain. The clinical implication of this is not clear and needs clarification. Participants were advised to avoid alcohol, caffeine and smoking on the day of the baseline and follow-up visits. There was however a notable difference as participants were required to fast for the follow-up visit as it involved a fasting blood test whereas this was not a requirement at the baseline scan, as the blood test had been taken at the screening visit which preceded the baseline scan by a few days. It is possible that a difference in the fluid volume may have had an impact on the aortic distensibility. The acute impact of fluid volume and blood pressure reduction has been documented in patients with end stage renal disease before and immediately after haemodialysis[235]. The improvement in aortic distensibility following dialysis (from 1.9 $cm^2 \cdot dyn^{-1}.10^{-6}$ to 2.6 $cm^2 \cdot dyn^{-1}.10^{-6}$) was driven by a large reduction in pulse pressure from 53 mmHg to 39 mmHg with similar diameters for the aorta as measured by echocardiography of the ascending aorta using the parasternal long axis view. In another study comparing elite rowers to sedentary controls it was noted that there was no significant difference in the aortic distensibility between the groups with the physically active rowers having numerically lower aortic distensibility in the TAA and ABA possibly suggesting that increased physical activity may not necessarily lead to an increase in the aortic distensibility [236].

The study was not sufficiently powered to look for significant LV mass change at the levels of risk factor reduction that I saw. Other potential explanations for this may include the modest reductions that may limit the power to show difference combined with a relatively short interval of 6 months. The subjects in the study were possibly too healthy. Volunteers taking part in such studies are generally motivated before taking part in the trial and the vast majority did not have evidence of ventricular hypertrophy at baseline, suggesting that control of factors such as BP, were good to start with or that the cohort did not contain patients with hypertensive heart disease. Had this been the case I may have seen more of a change.

In studies looking at LV mass reduction following bariatric surgery the change in weight were substantially greater then seen in my study. It should be borne in mind that the bariatric surgery is a high risk and invasive intervention but with excellent results in those who benefit [144,237].

CMR tolerability and repeat scanning

CMR and other surrogate markers are technically feasible in primary prevention studies of predominantly lifestyle factors in asymptomatic participants. I noted a relationship between measured risk factor changes and changes in surrogate markers including FRS, left and combined CIMT. However TAA and TDA distensibility also changed significantly but surprisingly in the opposite direction to what we predicted. This may partly be due to the modest changes that occur with lifestyle interventions and the relatively short duration of follow up of six months along with the points discussed above. To accurately identify long term beneficial effects of small changes in variables such as BP and weight a larger number of scans would be required to sufficiently power the study, but then challenges of sustainability of lifestyle behavioural changes will come into play.

In summary, CMR use is feasible in a primary prevention setting looking for changes following predominantly lifestyle interventions. It is generally well tolerated and anecdotally almost every subject noted that the follow up scan was

less daunting and acceptable than the first thus adding to the fact that CMR can be repeated in a safe manner without risk of radiation and tolerated well.

Limitations

Although improvements were seen in CVD risk factors, these were modest. The follow-up scan was performed at 6 months and included with participants in a fasted state, which was not necessarily the case at the baseline scan. A longer duration follow-up scan at one-year or longer may be required to allow time for structural and functional differences in this group. Inter-scan variability was not assessed and ideally this should have been done to provide a better understanding of the variability of measurements in order to more accurately power future studies. Although analysis was performed blinded to the intervention there was potential for bias as the physician and the participants were not blinded to the intervention during visits.

Conclusions

Multi- parametric CMR is feasible in primary prevention studies, however, change may not be seen if there are only modest improvements in risk markers. A larger cohort or a longer interval before repeat scanning may allow clinically significant changes to be seen. Further studies are needed before CMR and other surrogate markers can be routinely used in primary prevention studies. Personalised e-coaching did not show clinical effectiveness in risk reduction when combined with current SOC in this CMR sub-study using robust surrogate markers.

Chapter 9 – Summary of thesis and future prospects

The main focus of this thesis was to determine the clinical effectiveness of tailored e-coaching in reducing cardiovascular risk in a primary prevention cohort with moderate and high cardiovascular risk using robust cardiovascular imaging and functional surrogate markers to assess change over 6 months.

Through the HAPPY London study, I have demonstrated that personalised e-coaching, using a web-based information portal and motivational emails, does not show clinical effectiveness in cardiovascular risk reduction when combined with the current SOC in a high-risk primary prevention cohort. I showed that promoting primary prevention guideline recommendation through face-to-face counselling can produce modest but significant improvements in a number of different cardiovascular risk factors in the medium term. This can be achieved through changes in lifestyle factors including increasing physical activity and weight reduction.

I was able to schedule the appointments using an online booking tool, which also had an automated function that provided appointment reminders. This may have been one of the reasons for the low participant drop out with 94% of the study group completing follow up.

I demonstrated that CFPWV could be used as a cardiovascular surrogate marker in the assessment of behavioural change. I was also able to demonstrate that it is feasible to use other imaging markers including CMR (namely LV mass and aortic distensibility) and carotid ultrasound although evidence for change in these correlating with long-term prognosis needs to be demonstrated.

In the systematic review of the guidelines on cardiovascular risk assessment I found a number of guidelines that make recommendation on the assessment of risk and screening for cardiovascular risk factors. There were, however, considerable discrepancies in the guidelines with no consensus on optimum screening strategies or treatment threshold. I found no consistent agreement on which individuals would be classified as high risk to enable aggressive

interventions. In the context of setting up an effective e-coaching tool this would pose challenges and the tool would need to be modified according to the guideline adhered to in that population.

I did, however, find that most of the current guidelines from Western countries agree on many of the lifestyle advice and interventions that should be promoted, particularly for individuals deemed to be at high risk for developing CVD. This is useful to allow incorporation into an e-coaching tool.

I found that using CMR in a primary prevention clinical trail is feasible and generally well tolerated. The ideal surrogate marker to use in a short-term trial is not yet clear. There is limited data on the long-term prognostic effect of changes in surrogate markers and this needs further clarification to allow effective interpretation of change to guide patient management.

I did not test the impact that this information and motivational intervention would have if provided through mobile phone applications that allow easier access for the individual with additional monitoring and feedback through the use of inbuilt activity monitors and dynamic feedback. It would be useful to assess the effectiveness of these advanced tools to determine if they could be useful in shaping behavioural change. Alternative strategies could include simple text message reminders that would not require Internet access and provide encouragement as seen in smoking cessation and medication compliance studies.

I also did not test whether different amounts of information may affect behaviour change. It may be possible that with too much information people find it difficult to prioritise change. The number of questionnaires in the trial may have deterred people in the e-coaching group from actually using the web site. Future studies should limit the questionnaires and use activity monitors, for example, to assess physical activity change objectively.

For future work I plan to analyse the potential impact on behaviour change and CVD risk reduction from personality trait data (from the 'big five' questionnaire) and engagement with the e-coaching tool based on the number of times

participants logged in. I will also look at the impact of e-coaching on the quality of life. I also plan to compare the correlation between the oscillometric PWV from the Vicorder against the CMR derived PWV.

In summary, to my knowledge my study is the first RCT of a novel computer-tailored e-coaching approach to modify lifestyle and multiple cardiovascular risk factors in a high-risk primary prevention population to reduce cardiovascular risk measured using reproducible and accurate cardiovascular surrogate endpoints known to be associated with important cardiovascular outcomes. Addition of e-coaching to guideline based SOC does not have additional effectiveness. Currently, there is limited evidence to recommend widespread use of e-coaching in high risk primary prevention populations. Alternative strategies need to be identified to help determine how best to promote risk reduction in people at high risk of future cardiovascular events.

Chapter 10 - Personal contribution to the research

I was involved in the design of the study. I gained ethical and NHS Research and Development approval for the HAPPY London study. I applied and was successful in getting the study added onto the NIHR portfolio, which resulted in significant improvement in the recruitment of participants through funding from the NIHR to enable recruitment through primary care practices and for additional research nurse time to accommodate enrolment of the participants in a timely manner. I was responsible for training the research staff with the study protocol, performing Vicorder device measurements and carotid ultrasound scanning.

I saw all the participants during the baseline and 6 month follow up visit and a large proportion of those attending the screening and 3-month visit. As participants attended 3 of the visits fasting, I offered and on many occasions made the tea and toast for them. I was responsible for giving the tailored face-to-face advice to all participants at the baseline visit and showing participants in the e-coaching group how to use the HAPPY London web tool. I performed the vast majority of the CMR scans, carotid ultrasound scans and Vicorder measurements at baseline and follow-up.

I performed the statistical analysis with the guidance of Professor Petersen. I was responsible for the data analysis, writing the manuscripts and thesis chapter writing with the supervision of Professor Steffen Petersen. I also lead the 2 systematic reviews with the contributions from the Erasmus Medical College collaborators.

Publications arising from this work

Cardiovascular Risk Assessment: A Systematic Review of Guidelines.
Mohammed Y. Khanji, MB, Bach; Vinci's V.S. Bicalho, MD; Claudia N. van Waardhuizen, MSc; Bart S. Ferket, PhD; Steffen E. Petersen, DPhil; M.G. Myriam Hunink, PhD. Accepted for publication Annals of Internal Medicine August 2016

Comparative cost-effectiveness of non-invasive imaging tests in patients presenting with chronic stable chest pain with suspected coronary artery disease: a systematic review. C N van Waardhuizen, **M Khanji,** T S Genders et al., European Heart Journal: Quality of Care and Clinical Outcomes. Accepted for publication May 2016

Work submitted

European Association of Cardiovascular Imaging (EACVI) Position Paper: Comprehensive Review of Cardiac Magnetic Resonance (CMR) Normal values and Recommendations for Severity Grading of Cardiac Chamber Size. SE Petersen*, **M Khanji***, P Lancelot et al. European Heart Journal Cardiovascular Imaging
Joint first author

Cost-effectiveness of periodic risk assessment vs. the Polypill approach for prevention of cardiovascular disease: A modelling study. B Ferket, M Hunink, **M Khanji** et al – Awaiting submission outcome, Heart

Cardiac Magnetic Resonance Imaging (CMR) and Cardiac Computed Tomography (CCT): a Systematic Review of Meta-Analyses. M Sanghvi**, M Khanji**, F Pugliese et al. International Journal of Cardiology – Awaiting submission outcome

Manuscripts in progress

Impact of electronic coaching on cardiovascular risk reduction in a high-risk primary prevention population: The Heart Attack Prevention Programme for You (HAPPY) London Randomised Controlled Study. **M Khanji**, A Balawon, R Boubertakh et al.

Impact of electronic coaching on cardiovascular risk reduction in a high-risk primary prevention population - A cardiovascular magnetic resonance sub-study. **M Khanji**, A Balawon, R Boubertakh et al.

The Applicability Of Current Cardiovascular Risk Scores And Cardiovascular Surrogates In COPD: A Case-Control Study. I S Stone**, M Khanji (joint first author),** WY James et al.

Abstracts and posters

Cost-effectiveness of periodic risk assessment vs. the Polypill approach for prevention of cardiovascular disease: A modelling study. B Ferket, M Hunink, **M Khanji** et al – Accepted for poster presentation at American Heart Association Scientific Sessions for November 2016, New Orleans, USA.

Cardiovascular risk reduction using contemporary guideline recommendations: Outcomes of the Heart Attack Prevention Programme for You (HAPPY) London Study. **M Khanji**, A Balawon, R Boubertakh et al. BCS conference. June 2016, Manchester, UK.

The applicability of current global cardiovascular risk scores and cardiovascular surrogates in chronic obstructive pulmonary disease: A case-control study. **M Khanji**, I Stone, WY James et al. Journal of Cardiovascular Magnetic Resonance 2016, 18(S1):P134 SCMR conference January 2016. Los Angeles, USA.

A comparison of cardiac motion analysis software packages: application to left ventricular deformation analysis in healthy subjects. H Almutairi, **M Khanji**, R Boubertakh et al. Journal of Cardiovascular Magnetic Resonance 2015, 17(S1):P57 SCMR conference January 2016. Los Angeles, USA.

Elevated blood pressure without hypertrophy raises left ventricular ejection fraction, **M Khanji**, A Balawon, R Boubertakh et al. Journal of Hypertension 2015, Vol 33 S1 p. e46

Cardiovascular magnetic resonance feature tracking in patients with acute myocarditis and normal ejection fraction: potential for improved diagnosis and prognosis – Top 6 Moderated best oral poster session
M Khanji, M Javaid, S Mohiddin et al. Journal of Cardiovascular Magnetic

Resonance 2015, 17(S1):M7

Assessment of cardiovascular magnetic resonance aortic stiffness in patients with increased cardiovascular risk: role of traditional risk factors and lung hyperinflation. **M Khanji**, I Stone, A Balawon, et al. Journal of Cardiovascular Magnetic Resonance 2015, 17(S1):P398

Splenic switch-off, a potential novel marker of lack of adenosine response: relationship to heart rate response and demographic factors. A Lighton, M Koulouroudias, F Zemrak, C Manisty, J Moon, C Davies, R Boubertakh, **M Khanji** et al. Journal of Cardiovascular Magnetic Resonance 2015, 17(S1):P92

Splenic switch-off, a potential novel marker of lack of adenosine response: prevalence and measurement reproducibility. M Koulouroudias, A Lighton, F Zemrak, C Manisty, J Moon, C Davies, R Boubertakh, **M Khanji** et al. Journal of Cardiovascular Magnetic Resonance 2015, 17(S1):P122

Pre Scan Information, Good Communication and Music: The Patient's Perspective to Improving Cardiovascular Magnetic Resonance Tolerability., T Castiello, M. Westwood, et al. Eur Heart J Cardiovasc Imaging May 2014 doi:10.1093/ehjci/jeu085

Age and Gender Patterns of Referral for Stress Perfusion MRI. A 5-Year Comparison. **M Khanji**, T Newton, M Westwood et al. Eur Heart J Cardiovasc Imaging, May 2013 doi:10.1093/ehjci/jet070

Oral Presentations

Cardiovascular magnetic resonance feature tracking in patients with acute myocarditis and normal ejection fraction: potential for improved diagnosis and prognosis. **M Khanji**. Welsh Cardiovascular Society Spring Meeting. April 2016, Cardiff. Winner of Ian Williams Prize

Pros and cons of RCTs and systematic reviews. **M Khanji**. Clinical Trials Workshop. SCMR Scientific Session 2016. SCMR conference January 2016. Los Angeles, USA.

Impact of electronic coaching on cardiovascular risk reduction in a high-risk primary prevention population - A cardiovascular magnetic resonance sub-study. **M Khanji**. Oral presentation at EuroCMR conference, Florence, Italy May 2016.

Interpreting and Using Cost Effectiveness Analysis. Invited talk as conference faculty. **M Khanji**. Clinical Trials Workshop. SCMR/EuroCMR Joint Scientific Sessions 2015. Nice, France

Why is this Nurse Still Breathless after His Primary PCI? Should We Open it or Close It? **M Khanji.** Society of Cardiovascular Magnetic Resonance 16th Annual Scientific Session. San Francisco, USA 2013

Endomyocardial Fibrosis Masquerading as Metastatic Colorectal Tumour; CMR Tissue Characterisation and Perfusion Imaging Pivotal in Guiding Urgent Surgical Management (Top 4 submitted cases session)
M Khanji, EuroCMR conference 2014 Vienna, Austria

Teaching

Faculty member SCMR Scientific international conference. Los Angeles, USA, Jan 2016

Faculty member Clinical Workshop on CMR Stress Imaging. Barts Health NHS Trust, London, UK, Oct 2015

Faculty member Joint SCMR/ EuroCMR Scientific international conference. Nice, France, Feb 2015

Faculty member Clinical Workshop on CMR Stress Imaging. Barts Health NHS Trust London, UK, Oct 2014

Lead organiser CMR Introduction Course at Barts Health NHS Trust, Jan 2014

Faculty member Medical Decision Making Course, Erasmus Medical Centre, Netherlands , Mar 2014

Organised weekly CMR physics teaching. Barts Health NHS Trust, London, 2013-14

Faculty member Clinical Workshop on CMR Stress Imaging, Oct 2013

Prizes

Welsh Cardiovascular Society Ian Williams prize for best scientific abstract 2016

Best Charity Ambassador – Barts Health Hero's of 2013 – HAPPY London team (Team lead)

Short-listed for Best Charity Ambassador – Barts Health Hero's of 2015

Appendix

Search Strategy for Guidelines

The MEDLINE search syntax, as previously described, served as a basis for all search strategies. In brief, the syntax had the 3 following elements intersected by the Boolean term "AND": subject headings and free-text terms for the interventions about the health check contents (that is, risk assessment, screening, early detection, early diagnosis, early intervention, periodic evaluation, periodic examination, periodic check-up, prevention, and risk management), subject heading and free-text terms for the conditions that could define high risk for CVD and CVD outcomes that should be prevented (that is, arteriosclerosis, atherosclerosis, hypertension, hyperlipidaemia, diabetes, CVD, CHD, heart failure, and aortic aneurysm), and publication types and title words that cover the clinical practice guidelines (that is, practice guidelines, guideline, guidance, standards, statement, position paper, position stand, recommendation, and consensus).

The references retrieved from the search were considered guidelines if they met the definition of the Institute of Medicine. Only guidelines recommending cardiovascular risk assessment specifically aimed to prevent the first CVD event were considered. Guidelines were excluded if they did not contain recommendations involving the apparently healthy general adult population, were entirely focused on early detection of CVD only, were not produced on behalf of a professional organisation, or were not relevant or applicable to Western countries. Only guidelines published from 2009 onward were included; thus, only recent or current guidelines were selected.

Appendix: Search Example

CINAHL (EBSCOhost):

((MH "Cardiovascular Diseases") OR (MH "Aortic Aneurysm+") OR (MH "Myocardial Ischemia+") OR (MH "Arteriosclerosis+") OR (MH "Cerebrovascular Disorders+") OR (MH "Peripheral Vascular Diseases") OR (MH "Heart Failure, Congestive+") OR (TX (cardiovascular N3 disease*)) OR (TX (coronary N3 disease*)) OR (TX heart disease*) OR (TX (stroke* or cerebrovasc* or cva*)) OR

(TX (aort* N5 aneurysm)) OR (TX (abdominal N5 aneurysm)) OR (TX (thoracoabdominal N5 aneurysm)) OR (TX (arteri* N3 occlusi*)) OR (TX (arteri* N3 stenosis)) OR (TX (peripher* N5 occlusi*)) OR (TX (peripher* N5 arteri*)) OR (TX (peripher* N5 vascular)) OR (TX heart failure) OR (TX atherosclerosis) OR (TX arteriosclerosis) OR (MH
"Hypertension") OR (MH "Hyperlipidemia") OR (MH "Diabetes Mellitus") OR (TX hypertension) OR (TX hyperlipid?emia) OR (TX dyslipid?emia) OR (TX cholesterol) OR (TX diabetes) OR (TX metabolic syndrome))
AND
((MH "Cardiovascular Diseases/PC") OR (MH "Preventive Health Care") OR (MH "Health Screening") OR (MH "Risk Assessment") OR (MH "Cardiovascular Risk Factors") OR (MH "Early Intervention") OR (TX prevent*) OR (TX (risk N3 reduc*)) OR (TX (risk N3 manage*)) OR (TX (risk N3 managing)) OR (TX (risk N3 intervent*)) OR (TX (risk N3 assess*)) OR (TX early N3 interven*) OR (TX early N3 detect*) OR (TX early N3 diagnos*) OR (TX screen*) OR (TX (periodic N3 exam*)) OR (TX (periodic N3 evaluat*)) OR (TX (periodic N3 check*)))
AND
((PT Practice Guidelines) OR (TI guideline*) OR (TI guidance*) OR (TI (position paper or position stand)) OR (TI statement*) OR (TI recommendation*) OR (TI consensus) OR (TI practice parameter*) OR (TI standards))
NOT
((PT commentary) OR (PT letter) OR (PT editorial))
Limit results to English language

Appendix: Search Strategy for Similar Recent Relevant Systematic Reviews

1 systematic review.m_titl. (41410)
2 guidelines.m_titl. (34941)
3 (cardiovascular disease or hypertension or diabetes or cardiovascular risk or dyslipidemia).af. (593940)
4 1 and 2 and 3 (20)
5 limit 4 to (English language and yr="2009 -Current") (19)

Ethical Approval

NHS
Health Research Authority
NRES Committee London - Central
Skipton House
80 London Road
London
SE1 6LH

Telephone: 020 797 22560

21 February 2013

Dr Steffen Petersen
Advanced Cardiovascular Imaging, William Harvey Research Institute
Barts Health NIHR Biomedical Research Unit
The London Chest Hospital
Bonner Road
E2 9JX

Dear Dr Petersen

Study title:	**Heart Attack Prevention Programme For You (HAPPY) London - A Randomised Control Trial Assessing The Benefit of Tailored E-coaching in Reducing Cardiovascular Risk**
REC reference:	**13/LO/0094**
IRAS project ID:	**110655**

Thank you for your letter of 11 February 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the NRES website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the Co-ordinator Julie Kidd, NRESCommittee.London-Central@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management

permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Notification(s) of no objection have been received from local assessors for the non-NHS site(s) listed in the table below, following site-specific assessment (SSA).

I am pleased to confirm that the favourable opinion applies to the following research site(s), subject to site management permission being obtained prior to the start of the study at the site (see under 'Conditions of the favourable opinion below').

Research Site	Principal Investigator / Local Collaborator
The Heart Centre, William Harvey Research Institute Barts and The London, Queen Mary's School of Medicine and Dentistry	Dr Mohammed Khanji

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Advertisement	3 Posters V1	04 July 2011

Advertisement		
Covering Letter		09 December 2012
Evidence of insurance or indemnity: Ref: B1262F10102012		30 July 2012
GP/Consultant Information Sheets: GP Letter	1.0	24 August 2012
Investigator CV: Petersen		04 August 2012
Letter from Sponsor: Provisional Sponsorship		13 December 2012
Letter from Statistician: Statistician Steffen Petersen		16 August 2012
Other: Website Information		19 December 2012
Other: Letter from Funder: Barts and The London Charity		23 February 2011
Other: CV: Khanji		19 December 2012
Other: CV: Pugliese		17 August 2011
Participant Consent Form	1.1	28 November 2011
Participant Consent Form	2	06 February 2013
Participant Information Sheet	1.1	28 November 2012
Participant Information Sheet	2	06 February 2013
Protocol	1.1	28 November 2012
Questionnaire: Validated Questionnaire: RPAQ/EQDL/SF36v2		
Questionnaire: Non-Validated Questionnaire - The Big 5 Traits - Thomas Dohmen Questionnaire		19 December 2012
REC application	3.4	09 December 2012
Referees or other scientific critique report: Peer Review		29 June 2012
Response to Request for Further Information		11 February 2012
Summary/Synopsis: Flow Diagram	1.1	28 November 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

13/LO/0094	Please quote this number on all correspondence

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

pp

Dr John Keen
Chair

Email:NRESCommittee.London-Central@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Mr Gerry Leonard, Joint Research Management Office*

Patient Information Sheet

Participant Information Sheet

Heart Attack Prevention Programme For You (HAPPY) London – Research Trial Summary

We want to help you understand your risk of having a heart attack or stroke in the future and try and identify an effective way of reducing this risk.

- The risk of this happening to you is largely based on your inherited genes, your current state of health, your lifestyle and your age.

Why are we asking you to take part?

- If you are aged between 40 and 74 and estimated as having a moderate to high risk of having a heart attack or stroke during the next 10 years then we would like to try and reduce this risk. This risk is calculated after filling out the mini-check questionnaire on the Happylondon.info website.

Who are we?

- Researchers at the William Harvey Research Institute which is a part of Queen Mary University of London along with Barts Health NHS Trust. This study is part of an academic programme.

What are we asking you to do?

- Fill in 4 questionnaires
- Attend a health centre 4 times over 6 months
- Follow lifestyle advice for 6 months (Half of the study group will get this via the internet for 6 months (e-coaching))
- Maybe undergo an MRI scan on your heart. (A small number of participants out of the 400 selected)

What do you get out of it?

- A heart-focused medical examination by an expert
- Free coaching aimed at trying to make you healthier
- The chance to potentially live a better quality life
- The satisfaction of helping us to improve our understanding of health and care for others

Is it confidential? YES

THE DECISION IS YOURS – IF YOU ARE INTERESTED PLEASE READ THE DETAILED PARTICIPANT INFORMATION SHEET BELOW

1. **Invitation**

You are being invited to take part in a clinical trial. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others, e.g. your family and friends, if you wish. Please ask us if there is anything that is not clear or if you would like more information (phone numbers are given at the end of this sheet). Take time to decide whether or not you wish to take part.

Thank you for reading this.

2. Why is this study being carried out?

Diseases of the heart and blood vessels, such as heart attacks and strokes, are very common and can lead to severe disability or death. Changes in the body leading to heart attacks and strokes usually develop over decades as a result of smoking, diet, and lack of exercise, obesity, diabetes and high blood pressure. Changes in life-style and diet can significantly reduce the risk of heart diseases. Your General Practitioner will invite 40 to 74 year olds who have no known heart disease to take part in the NHS Health Check, which measures each person's individual risk of developing a heart attack or stroke and encourages them in a face-to-face meeting to take part in programmes to help them to give up smoking, lose weight etc. where necessary.

In this new study we will test whether individualised e-coaching via email or the Internet can help people to make the necessary changes in their life style to reduce the risk of heart attacks and strokes.

3. Why have I been chosen?

You have been approached because according to information about your health and lifestyle you provided you are at moderate to high (>20%) risk of developing a heart attack or stroke over the next 10 years. This is an estimated risk, not your actual risk, based on the Framingham Heart Study. E.g. if your risk is 20% or more you have an estimated 2 in 10 chance r more of developing a heart attack or stroke over the next 10 years.

Altogether, 400 participants like you will take part in the clinical trial.

4. Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and you will be asked to sign a consent form at your first visit to one of our centres. Even after consenting you are still free to withdraw at any time and without giving a reason (If you would give us a reason it would be valuable for us to understand participants' research

experience). A decision to withdraw at any time, or a decision not to take part, will have no adverse consequences. In particular it will have no implication on your current or future medical care.

There will be no payment for taking part in the study. We will however refund your travel expenses at each visit within Greater London, on provision of receipts.

5. What will happen to me if I take part?

You have already completed the internet based form (www.happylondon.info), which helped us to estimate your ten-year risk of developing heart attacks or strokes.

Here is a summary of what we are asking you to do over a period of 6 months:

- Attend our Centres 4 times over the 6 months. At the first visit you will be given an explanation of the study and you will have the chance to ask any questions about it, before signing a consent form.
- Have your height, weight and waist circumference measured at the beginning, middle and at the end of the study.
- Have your blood pressure and blood vessels assessed at the beginning and at the end of the study.
- Give a blood sample at the beginning, middle and at the end of the study.
- Complete questionnaires to determine your quality of life, general well-being, and physical activity at the beginning and at the end of the study.
- Complete questionnaires about your personality, including your attitudes towards risk (economic preferences) at the beginning of the study.
- Only some participants undergo a magnetic resonance (MRI) scan of your heart and blood vessels at the London Chest Hospital or Barts Hospital (depending on availability) twice: at the beginning and at the end of the study.
- **If you are a smoker or ex-smoker you may be asked to perform lung function tests which will measure how well your lungs are working.**
- Use your HAPPY London website as often as you like, if you are allocated to that group, for latest health news and for checking on your progress on changing your life style etc.

The following paragraphs describe what will happen to you in more detail. This information is summarized in the table on page 6.

This study is a randomized clinical trial, which means that if you decide to take part in our study you will be allocated at random to one of two groups. The first will receive **standard care** (getting one off advice following the blood test, weighing etc.)

and the second will receive **standard care and get access to Happy London** tailored e-coaching.
You will need to come to the centre on four occasions. The basic study is summarised below:

You will be invited initially to visit the Heart Centre at the William Harvey Research Institute, Charterhouse Square and the study will be explained to you. If you wish to take part you will be invited to sign the consent form. We will then interview you about your medical history and ask you to complete short questionnaires about your physical activity, quality of life, general well-being and personality. We will measure your blood pressure and using a very similar technique we will measure the stiffness of your blood vessels. We will take blood samples and do similar tests to the ones you would get from the NHS Health Check: total cholesterol, good (HDL) and bad (LDL) cholesterol, triglycerides (these are all related to fat circulating in your bloods), fasting blood sugar (which could detect diabetes or tendency to develop diabetes) and Creatinine (a measure of kidney function).

Blood samples will be taken through a needle inserted into a vein in your forearm or back of your hand. 20 ml of blood will be taken on this occasion. We will take the same amount of blood on the last visit. Hence 40 ml of blood will be taken during the entire study, which will include taking blood at the screening visit. Blood samples may be stored until the project is deemed complete to allow us to perform additional blood tests (e.g. special proteins), although most analyses will be performed shortly after collection.

We would like you to come to us without having eaten any food for at least 8 hours. We anticipate that this visit will take approximately 1 hour in total. All of these procedures are harmless and, barring the blood sample, painless.

We will repeat the same measurement after 3 and 6 months.

If you are one of the first 130 participants we will also invite you to come to the London Chest Hospital or Barts Hospital and undergo a magnetic resonance (MRI) scan of your heart and blood vessels shortly after the first visit and before you start your e-coaching programme. During this scan we will insert a small cannula (tube) in your vein and inject a dye to better visualise the heart. This substance has very low risk of side effects. There are some factors which would mean that you should not undergo magnetic resonance imaging and we routinely check for these (e.g. if you have a pacemaker, defibrillator, vascular clips, cochlear implants, kidney failure or significant claustrophobia). You do not in any case have to agree to have the MRI done, but it helps us to evaluate how valuable MRI may be for assessing the success of e-coaching in future similar studies.

The consent form will ask you if you are willing for us to store a sample of your blood for future research by our institute and our research partners. This is not compulsory. Samples will not be sold or given to commercial bodies. Any other use that we may want to make of your sample will require approval by a Research Ethics Committee, which is an independent panel of experts who assess all research projects for safety, ethical acceptability and who protect volunteers' interests. None of the work that we envisage doing will have any direct implications for your personal health.

We will use information held by the NHS, your General Practitioner and records maintained by the Office for National Statistics (ONS) to follow up your health status during the study.

The ONS is a national database that covers statistics relating to information gathered on public health, health services provided by the National Health Service (NHS), social care, and health and safety at work.

6. What else do I have to do?

You will need to tell us if you suffer from any medical conditions or if you are taking any medication, as this may exclude you from the study.

You will need to have "good" access to Internet every day so that you can take advantage of the personal advice you will receive through your Happy London web profile.

7. What is being tested?

We are testing a new method of helping people to reduce their risk of developing heart attacks and strokes by giving them personal coaching using modern technologies like Internet and email.
For half of the group, that will be asked to use the website actively, they will be able to view their lifestyle and health scores and will be able to view educational material that will be personalised and relevant to them. They will also receive regular emails with useful information towards leading a healthier lifestyle.

8. What are the possible disadvantages and risks of taking part?

The techniques used in this study are inherently safe and widely practised. You may however have minor pain and/or bruising after blood-taking.

Extremely rarely, people may experience nerve and muscle twitching during an MRI scan. If you are participating in the MRI sub-study, then the MRI scan is a very precise way of investigating organs (including heart and blood vessels) and is very safe as it

does not use radiation (such as X-rays) and can be performed many times without a risk of causing harmful effects. There are very small risks of side effects from the MRI contrast agent if your kidney function is normal or almost normal (and we will check your kidney function prior to the scan). As already stated, having an MRI scan is not obligatory.

Assessments	Visit 1 (day 0) Eligibility check	Visit 2 (1 day-2 weeks)	Visit 3 at 3 months	Visit 4 at 6 months
Consent	X	-	-	-
Check for MRI safety	X	X	-	X
Weight/height etc	X	-	X	X
Heart disease risk factors	X	-	X	X
Blood pressure measures	X	-	X	X
Fill in Questionnaires		X	X	X
Blood test	X	-	X	X
Ultrasound of neck and leg blood vessels		X		X
Heart scan in a selection of participants (Cardiovascular MRI scan)		X		X
Lung Function Tests in a selection of patients		**X**		

Table 1 – Overview of visits and investigations

9. What are the possible benefits of taking part?

This study may not benefit you directly, however if the method we are testing works you would benefit from reducing your risk of developing heart attacks and strokes. However, during the study you will learn about healthy lifestyle and the state of your heart health.

10. What if something goes wrong?

The chances of any harm befalling you in this study are very small indeed. However, Queen Mary University London (QMUL) has provided insurance against negligent harm and if you are harmed through fault on the part of the investigators, you will be entitled to compensation.

Queen Mary University London (QMUL) cannot provide insurance for non-negligent harm. If you are harmed by taking part in this study and it is not the fault of the Investigators, then you may have grounds for a legal action but you may have to pay for it.

Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during this study, then you should first of all discuss this with Dr Khanji, Dr Petersen or Dr David Collier. If you would rather discuss any problems with individuals independent of the study at QMUL / Barts Health NHS Trust you can contact the Patient Advice and Liaison team (PALS). Contact information is given on the last page.

11. **Will my taking part in this study be kept confidential?**

All the information that is collected about you during the course of the study will be kept strictly confidential and will be kept in a locked room and stored on a password-protected computer. Only the investigators and the website admin staff who will deal with the technical issues of the website will have access to the data. The website is designed with strict security measures to protect your personal data. Any information about you that leaves the centre will have your personal details removed so that you cannot be recognised from it. Data protection will be in place.

Your GP will be notified of any important results in the study, unless you tell us not to in the consent form.

12. **Can I withdraw from taking part during the study?**

You are free to withdraw from the study at any point. We would ask you to inform Dr Khanji or Dr Petersen of your decision so that we remove you from the study list and we will not collect or use any further information about you from that point.

13. **What will happen to the results of the research study?**

The results from each volunteer will be pooled to obtain average results, so that no individual or their results will be identifiable in any form of publication. The results from the research will be presented locally and internationally to other medical colleagues. The results will also be written up as a full paper and be submitted for publication in an international journal. **Some of the baseline results from this study may be pooled and compared with results from a different trial.** These events will most likely occur 1-2 years after your participation in the study. If you would like a copy, let us know and we can email you a copy when it is published.

14. **Who is organising and funding the research?**

The research is being organised by the William Harvey Research Institute which is a part of QMUL along with Barts Health NHS Trust. Experienced doctors and nurses allocated to undertake research will be performing it. The study is funded by The Barts and The London Charity.

None of the doctors will be paid for including you in this study.

15. **Who has reviewed the study?**

The London Central National Research Ethics Service Committee has reviewed this study.

16. **Contacts for Further Information**

You can contact an investigator to discuss your concerns and/or to get help:

Dr Mohammed Khanji, Centre for Advanced Cardiovascular Imaging at the London Chest Hospital, Bonner Road, London, E2 9JX
Telephone number: 020 7882 6919; Email: m.khanji@qmul.ac.uk

or

Dr Steffen Petersen, Centre for Advanced Cardiovascular Imaging at the London Chest Hospital, Bonner Road, London, E2 9JX
Telephone number: 0207 882 6902; Email: s.e.petersen@qmul.ac.uk

Dr David Collier, William Harvey Heart Centre, Clinical Pharmacology, Charterhouse Square, London EC1M 6BQ
Telephone number: 07961 383925; Email: d.j.collier@qmul.ac.uk

Alternatively, you may wish to speak to someone who is independent of the study (not actively involved). We suggest:

Patient Advice and Liaison team (PALS) provides free and confidential information to patients/ families/ carers. They provide information and advice regarding any issues or concerns that you may have**.** Telephone number– 020 3594 2040 (based at The Royal London Hospital)

Thank you for considering participating in this study!

You will be given a copy of the information sheet and a signed consent form to keep.

Study Consent Form

WRITTEN CONSENT FORM: REC Number: 13 / LO / 0094 ver 2.0 06/02/ 2013

Barts and The London School of Medicine and Dentistry

Barts Health NHS Trust

STUDY CONSENT FORM

Thank you for reading the information sheet about the 'Happy London' trial. Please read this consent form carefully and put your initials in the boxes by the items to which you agree or give your consent. Please put a line through the box if you do not wish to give your consent to a particular item.

Title of research proposal: **Happy London**

Please initial text box: Example

SP (Correct) ✓ (Incorrect)

HAPPY LONDON

Patient Identification Number:

	YES	NO
1. I confirm that I have read and understand the **Happy London**– Version 2.0 Participant information sheet **dated February 06, 2013**, for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐	☐
2. I understand that my participation of the ***HAPPY London Trial*** is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐	☐
3. I give permission for long-term storage and use of my blood samples for health-related research purposes (even after my incapacity or death), and relinquish all rights to these samples which I am donating.	☐	☐

When completed, 1 for Research Subject and 1 for researcher site file (original)

	YES	NO
4. I give permission for full access to my past, present and future medical and other health-related records, and for long-term storage and use of this and other information about me, for health-related research purposes (even after my incapacity or death).	☐	☐
5. I give permission for my data from this trial to be used in conjunction with data from other clinical trials by this research team for health-related research purposes	☐	☐
6. I give permission for my GP to be informed about me taking part in this Trial and about important result in the study relating to my health.	☐	☐
7. I understand that information held by the NHS, my General Practitioner, and records maintained by the Office for National Statistics (ONS) may be used to follow up my health status, I give permission for this information to be obtained from the ONS, the NHS and/or my GP if necessary.	☐	☐
8. I understand that all research data will be treated confidentially. All data will be stored securely at the study coordinating centre. Data will be anonymised in any publications. I understand that for the purpose of the website there will be information about me which will be protected by the website service provider (e.g. email address, name contact number).	☐	☐
9. I understand that I may be contacted again by the study team (e.g. to answer some more questions and/or attend another assessment visit), but this is optional.	☐	☐
10. I agree to take part in the above trial.	☐	☐

_____	_____	_____
Name of Participant (CAPITALS)	Date	Signature
_____	_____	_____
Name of Person taking consent (CAPITALS	Date	Signature

When completed, 1 for Research Subject and 1 for researcher site file (original)

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